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Review

# Probing and Regulating Dysfunctional Circuits Using Deep Brain Stimulation

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Despite the best available medical treatments, many patients continue to be disabled by neurologic and psychiatric disorders, resulting in a large unmet need. Advances in imaging and neurophysiology over the last two decades have led to a reinterpretation of some neurologic and psychiatric conditions as primarily disorders of circuit function, or "circuitopathies." These developments have been accompanied by advances in neurosurgical techniques with the increasingly widespread utilization of deep brain stimulation (DBS) to recalibrate dysfunctional circuits. The versatility of DBS as both a probe and modulator of neural circuits is making it a powerful tool to study the human brain, helping provide important details of the pathophysiology of circuit dysfunction. We are currently in a phase of active investigation to determine which circuits and disorders could be treated with DBS. Here we review recent advances in the DBS field and discuss potential future directions in targeted intracranial neuromodulation.

## Introduction

The burden of neurological and psychiatric illness in society is substantial and will increase at a rapid rate in the next few decades (WHO, 2004). While our understanding of the specific causes and consequences of disorders affecting the human cerebrum is still at an early stage, recent developments in brain imaging and neurophysiology have led to important insights into the mechanisms underlying the clinical manifestations of these disorders. Such studies have provided strong evidence that many of the signs and symptoms we see in patients arise as a consequence of disordered activity in neural circuits (Bonelli and Cummings, 2007). This supports the notion that the clinical manifestations in patients with common neurological and psychiatric conditions, for example, Parkinson's disease (PD), major depressive disorder (MDD), and Alzheimer's disease (AD), reflect underlying dysregulation and malfunction in specific brain networks subserving motor, mood, and cognitive function, respectively (Dickerson and Eichenbaum, 2010; Price and Drevets, 2010; Shin and Liberzon, 2010; Wichmann et al., 2011).

The etiologies of circuit disturbances are varied and include damage to neural pathways, loss of neural elements and populations, as well as disturbances in the functional activity of neural circuits, through disordered firing and pathological oscillatory activity in neuron ensembles. These disturbances can be temporary or permanent, intermittent and paroxysmal. They can affect multiple spatially and temporally separated cerebral circuits and produce a great variety of behavioral readouts that help clinicians diagnose, classify, and treat. It is convenient to think of a "symptomatotopy" with each of the individual elements in the constellation of symptoms in these complex disorders mapping onto a specific neural circuit or subcircuit.

The introduction of electrodes and the application of therapeutic electrical stimulation within dysfunctional circuits not only allow alleviation of symptoms but also present the unique opportunity for probing the function of these circuits. In so doing, deep brain stimulation (DBS) offers a portal into the workings and dynamics of brain circuits in relation to behavior and cognition. For certain patients who have failed conventional therapies, DBS can provide striking benefits (Holtzheimer and Mayberg, 2011; Hariz, 2012). As a result, the promise of DBS has led to its widespread investigation. According to Medtronic, a prominent supplier of DBS devices, the number of patients that received surgery is estimated to have exceeded 100,000 worldwide. Notably, the realization of the shared underlying pathological processes at work and the examination of DBS as a potential treatment for a large number of brain disorders have contributed to a rapprochement of the hitherto arbitrarily separated fields of neurology and psychiatry. It has also contributed to a scientific renaissance in systems neuroscience. What was a relatively obscure field 30 years ago is now an area of active scientific enquiry with over 700 DBS-related manuscripts being published yearly (Figure 1). Here we outline the current state of knowledge of DBS, including what is known about its mechanisms of action as well as how it has been used to study and modulate activity in dysfunctional neural circuits in patients with neurological and psychiatric disorders.

## What Is Deep Brain Stimulation?

The implantation of DBS electrodes is a neurosurgical procedure, often performed under local anesthesia with patients fully awake to facilitate precise stimulation mapping. After placement of the electrodes in the desired target below the convexity of the brain, they are connected to a programmable pulse generator, similar to modern cardiac pacemakers, that is implanted under the skin below the collarbone. Once implanted, DBS devices can be accessed externally and stimulation settings titrated to clinical effects. Electrical stimulation can be finely adjusted to maximize clinical benefits and avoid off-target spread of current or unwanted adverse effects. Modifiable variables include the selection of the optimal contact within the electrode array, the

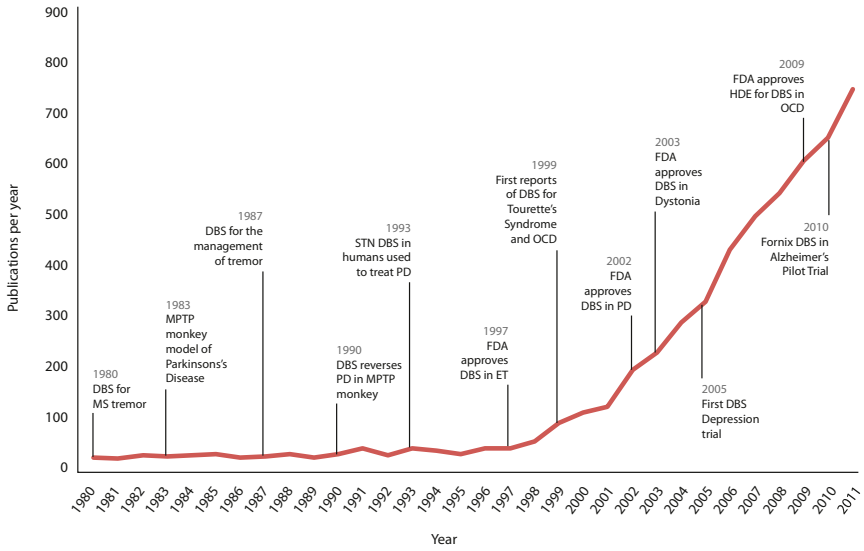



**Figure 1. Yearly Growth in the Number of DBS Publications from 1980 to 2011**

Significant DBS milestones since 1980 are shown superimposed on the graph. MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; STN, subthalamic nucleus; PD, Parkinson's disease; FDA, Food and Drug Administration; HDE, Humanitarian Device Exemption; ET, essential tremor; OCD, obsessive-compulsive disorder; MS, multiple sclerosis.

choice of bipolar or monopolar stimulation, the frequency of stimulation (typically in the high-frequency range [130–180 Hz] for most contemporary applications), amplitude, and pulse width. The stimulation can also be rapidly cycled on and off for fractions of a second to several seconds. Most commonly, stimulation is delivered continuously around the clock. An important feature is that DBS therapy can be masked, with patients randomly assigned to either stimulation "ON" or "OFF" in a blinded fashion. This design, allowing either active or sham stimulation, facilitates double-blind controlled clinical trials, in which the effect of placebo and microlesioning from electrode insertion can be assessed (Mallet et al., 2008; Holtzheimer et al., 2012). Depending on the settings, the implanted batteries can last up to 4 or 5 years. For clinical indications requiring high outputs leading to more rapid battery depletion, rechargeable pulse generators are now also available.

In assessing the risk-benefit balance, it is important to know that DBS can also be associated with important operative and perioperative risks. DBS adverse effects can be related to the surgical procedure, to the application of stimulation, or to the long-term consequences of implanted hardware. Serious or life-threatening adverse events, such as brain hemorrhage, are rare, occurring in less than 1%–2% of patients, with less serious, typically reversible events, such as wound infection and stimulation-related side effects, occurring in up to 9% of patients (Hamani et al., 2008).

The importance of DBS to neuroscientists stems primarily from its duality as both a probe and modulator of neuronal activity (Lozano et al., 2010). During physiological mapping for the selection of the optimal brain target for electrode placement, surgeons can record activity from single or populations of neurons, at rest as well as in response to various motor and cognitive tasks (Davis et al., 2005; Androulidakis et al., 2008; Sheth et al., 2012). This is generating a wealth of data that is advancing our understanding of the anatomy and circuitry of neurological and psychiatric conditions. Microelectrode recordings along brain trajectories in awake humans allow the identification of electrophysiological signatures of target neurons and reveal how they are involved in regulating diverse functions such as movement (Hutchison et al., 1998), pain (Hutchison et al., 1999), reward (Zaghloul et al., 2009), decision making (Sheth et al., 2012), and plasticity (Davis et al., 1998). Another opportunity comes from the ability to have the DBS electrodes externalized and to record local field potentials from DBS contacts placed within deep brain structures. This approach is leading to important findings including characterization of pathological activity such as beta oscillations in the subthalamic nucleus (STN) of PD patients (Kühn et al., 2008), how basal ganglia nuclei are involved in movement planning and execution (Paradiso et al., 2004), and how certain DBS targets are involved in emotional processing (Brücke et al., 2007).

Therapeutically, stimulating neuronal populations and elements to alter pathological baseline activity and thereby influence local, regional, and up- and downstream projections is the central unifying principle of DBS treatment regardless of clinical indication. A theoretically effective target, therefore, is defined by its relative prominence, functional connectivity, and role within a circuit driving the target behavior or symptom. Tracking the behavioral and molecular consequences of stimulation within these pathological circuits is providing a rich opportunity for discovery.

## History of DBS

The first neurosurgical interventions to alleviate abnormal movements or psychiatric disturbances involved the severing or ablation of neural pathways. Victor Horsley, having performed removal of the motor cortex to treat chorea (Horsley, 1890), achieved cessation of the abnormal involuntary movement (albeit by producing paralysis) and is generally regarded as the father of functional neurosurgery. In 1935 at the second International Congress of Neurology in London, UK, James Fulton described that making lesions in the frontal lobes of nonhuman primates resulted in the attenuation of aggressive behavior. Portuguese neurologist Egas Moniz, who attended the meeting, returned to Lisbon, where with neurosurgeon Almeida Lima, he rapidly translated this procedure to psychiatric patients, producing striking improvements in their aggressive behavior (Moniz, 1936). These pioneering operations, in an era in which there were little treatment options, led to the widespread use of neurosurgery to treat psychiatric disturbances and eventually to the awarding of the 1949 Nobel Prize in Medicine and

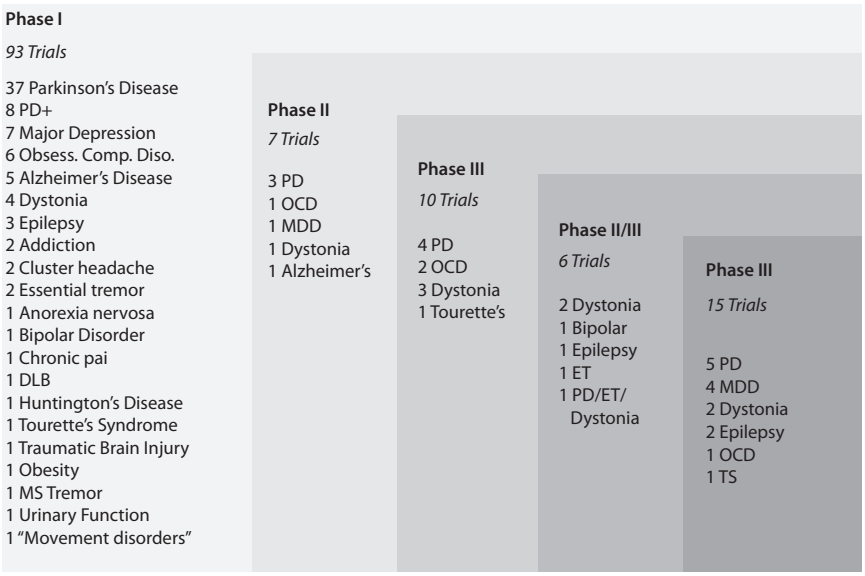



**Figure 2. Registered Phase I to Phase III DBS Trials that Are Ongoing and Enrolling Patients, as of September 2012**

A phase I trial tests a new drug or treatment for the first time in humans and is primarily a safety and feasibility study. A phase II trial expands the phase I trial to a larger group of patients to test for possible efficacy. A phase III trial tests a new treatment against a placebo and/or a currently accepted "gold-standard" treatment, in order to establish the efficacy of the new treatment and to make recommendations on its use. All data were obtained from the United States National Institutes of Health (http://www.clinicaltrials.gov). PD+, Parkinson's disease plus an additional disorder (tremor, depression, dystonia); DLB, dementia Lewy body; MDD, major depressive disorder; TS, Tourette's syndrome; MS, multiple sclerosis; PD, Parkinson's disease; OCD, obsessive-compulsive disorder; ET, essential tremor.

Physiology to Moniz. The invention and application of human stereotactic frame-based surgery made possible more precise interruption or ablation of neural structures starting in the 1940s (Spiegel et al., 1947). Over the next three decades, stereotactic surgery was applied principally to make lesions in basal ganglia and thalamic nuclei in patients with movement disorders, following the principle of "neutralizing" brain areas that generate or propagate pathological outputs. A number of procedures, chief among them pallidotomy, thalamotomy, and subthalomotomy, were found to alleviate various signs and symptoms of Parkinson's disease, including tremor, rigidity, and akinesia, without producing the paralysis that accompanied earlier operations involving interruption of the corticospinal system.

Subsequent years, however, saw a decline in the number of procedures performed for PD and psychiatric conditions, with functional neurosurgical procedures all but disappearing. This was due to two developments that continue to shape the application of neuromodulation technology today, namely the development of effective medications, such as chlorpromazine and levodopa in the 1950s and 1960s, as well as the mounting backlash against the unchecked misuse of psychiatric surgery. By the 1980s and 1990s, however, it became clear, particularly for PD, that many patients showed insufficient benefit with medical therapy and continued to be disabled or developed medication-related adverse effects. These developments, coupled with a better understanding of neural pathophysiology, improved technology, and advances in brain imaging, have led to a reappraisal and "renaissance" of functional surgical approaches and paved the way for DBS.

While the therapeutic uses of electrical stimulation for neurologic and pain disorders dates back to the use of electric eels in ancient Egypt (Henderson, 2008), the modern era starts with the implantation of electrodes in laboratory animals in the 1940s and 1950s and experiments on the behavioral effect of electrical stimulation (Delgado and Livingston, 1948; Olds and Milner, 1954). From there, there was rapid translation into human research, with the application of DBS through temporary electrodes and external pulse generators in patients with neuropsychiatric and pain disorders (Heath et al., 1955; Heath, 1963; Bishop et al., 1963; Schaltenbrand, 1965; Mazars, 1975; Bechtereva et al., 1975; Richardson and Akil, 1977). An additional impetus for the transition from "ablation to stimulation" was based on the observation during surgery that high-frequency electrical stimulation applied for brain mapping prior to lesioning could cause an immediate cessation of tremor in patients with Parkinson's disease (Benabid et al., 1987). The similar physiological effects obtained with stimulation or lesioning led early on to the idea that electrical stimulation produced a "reversible lesion" of target structures.

The current era of DBS has been driven principally by advances in the treatment of movement disorders, particularly PD (Figure 1). The discovery of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its use in developing a nonhuman primate model of PD was a new launching point for modern experimental surgical therapies using focal lesions and electrical stimulation to disrupt the pathological activity that emerges with dopamine depletion and thus restore function (Bergman et al., 1990; Aziz et al., 1991, Benazzouz et al., 1992). These seminal observations were rapidly translated to patients, with thalamic DBS for essential tremor approved by the Food and Drug Administration (FDA) in 1997 (Benabid et al., 1987; Koller et al., 1997; Zhang et al., 2010). DBS of the subthalamic nucleus or globus pallidus (GPi) for the management of PD was approved in 2002 (Limousin et al., 1998; Follett et al., 2010). A Humanitarian Device Exemption was granted by the FDA for DBS for dystonia in 2003 and for DBS of the anterior limb of the internal capsule for obsessive-compulsive disorder (OCD) in 2009. With the realization of the relative safety and therapeutic effects of DBS, it has now become a mainstream surgical procedure. The cumulative experience of DBS is now being leveraged and applied to different brain circuits to study DBS as a potential treatment for other patient populations. A brief enumeration of potential indications being pursued for DBS and the stage of clinical investigation for the various disorders is shown in Figure 2.

**Table 1. Possible Contributions to Pathophysiology of Circuit Dysfunction in Neurological and Psychiatric Disorders**

| Dysfunction | Example(s) |
|---|---|
| Change in the balance of excitation and inhibition | Epilepsy (Engelborghs et al., 2000), PD (Alexander et al., 1986), and schizophrenia (Lisman, 2012) |
| Increased firing, increased bursting, increased synchrony, and loss of specificity of receptive fields | PD and dystonia (Lozano et al., 2002; Filion and Tremblay, 1991; Lenz et al., 1999) |
| Abnormal oscillations | Four to eight hertz oscillations producing tremor, beta oscillations mediating akinesia in PD (Little and Brown, 2012), alpha in PPN in PD (Thevathasan et al., 2012), and gamma in schizophrenia (Lisman, 2012) |
| Thalamocortical dysrhythmia | Tinnitus, PD, and various neuropsychiatric disorders (Llinás et al., 1999) |
| Hyper/hypoactivity of specific nodes within networks | SCC/Area 25 in MDD (Mayberg et al., 2005) and hippocampus in schizophrenia (Kühn and Gallinat, 2011) |
| Deficits in corollary discharge | Schizophrenia (Lisman, 2012) |
| Default mode dysfunction, dysfunctional cerebral glucose utilization | Alzheimer's disease (Greicius et al., 2004; Laxton et al., 2010) and depression (Sheline et al., 2009) |

STN, subthalamic nucleus; PD, Parkinson's disease; PPN, pedunculopontine nucleus; SCC, subcallosal cingulate; MDD, major depressive disorder.

## The Nature of Circuit Dysfunction and Its Treatment with DBS

The therapeutic premise of DBS is the modulation of pathological activity within brain networks. Brain network organization and structure, however, is intrinsically complex, with a number of characterizing features including small-world topology, highly connected hubs, and modularity as revealed, for example, using graph theory analysis (Sporns et al., 2002; Sporns, 2011). Further, the identification of the networks and their constituent elements is not only challenging, but the nature of the network disturbances and their precise localization and dynamic properties are also incompletely understood. A number of guiding principles are emerging however. First, what can start as focal and relatively well-localized disturbances in neuronal function can be transmitted through the brain to mono- and polysynaptically connected structures and regions. This can result in widespread dysfunction throughout an entire neural network, engaging large cortical and subcortical territories, leading to pathological changes in function and behavior. Second, structural and functional neuroimaging as well as electrophysiological investigations have helped identify and characterize these disturbances and have pinpointed examples of circuit dysfunction and some accessible critical nodes. Third, in some cases, neutralizing, disrupting, or, on the other hand, driving activity at these sites can reestablish the functional integrity and ultimately the effective output of the involved circuits leading to a clinical benefit (Lozano et al., 2008). Two seemingly opposite strategies, either driving activity in underperforming circuits or reducing activity in overactive or "error signal generating" regions may lead to clinical improvements (Mayberg et al., 2005; Laxton et al., 2010). Fourth, the clinical effects of DBS depend on changes that are both immediately adjacent and remote to the area being stimulated and can occur both acutely and in a delayed and progressive fashion.

While current evidence suggests that circuit dysfunction is common to most neurological and psychiatric illnesses, this is still somewhat speculative and far from being established for many conditions and the exact or presumed nature of the dysfunction across disorders and its influence on brain function and behavior can vary significantly (Table 1). Several theories have been posed, which have helped furnish proposed models of pathophysiology for some of the most common brain conditions (Table 2). Importantly, circuit dysfunction models have provided the impetus for brain-based, precisely targeted interventions, whose objective is rebalancing or restoration of circuit activity. While these general principles may apply across a variety of disorders, here they are illustrated by focusing the discussion on prototypical conditions affecting motor, mood, anxiety, and cognitive circuits: Parkinson's disease and other movement disorders, major depressive disorder, obsessive-compulsive disorder, and Alzheimer's disease, with the realization that there are a variety of other disorders that are newly being considered as therapeutic targets for DBS (Figure 2).

### *Parkinson's Disease, Other Movement Disorders, and Motor Circuits*

PD is among the most common neurodegenerative conditions, with a prevalence of 1% in adults over the age of 60 (de Lau and Breteler, 2006). Despite the availability of several classes of medications, most commonly targeting the loss of dopamine that is a hallmark of the illness, there remain no enduring and effective disease-modifying treatment options for the illness. Patients experience progressive motor symptoms that become associated with medication-induced motor complications (motor fluctuations and drug-induced dyskinesias), psychiatric disturbances (impulse control disorders, depression, and hallucinations), cognitive deficits, and dementia in advanced disease (Lang and Lozano, 1998).

Experiments in MPTP-treated nonhuman primates have shown that dopaminergic neuronal loss produces profound disturbances in the function of various nuclei in the basal ganglia including increased firing, increased bursting, increased synchrony, and correlated activity in specific frequency bands, as well as a tendency toward loss of specificity in neuronal receptive fields (Mitchell et al., 1987; Filion and Tremblay, 1991). The propagation of these disturbances throughout cortico-striato-thalamic-cortical (CSTC) motor loops (Figure 3A) is thought to be largely responsible for the major motor manifestations of PD, which include tremor, rigidity, akinesia, and postural and gait abnormalities (Wichmann and Delong, 2007). Despite our increasing knowledge of the various components of this circuitry, how these changes in neuronal behavior produce clinical symptoms is not well understood. Current hypotheses are many and include that localized groups of neurons firing in

**Table 2. Neural Circuit Disorders and Postulated Circuit Dysfunction**

| Disorder | Circuit | Postulated Circuit Dysfunction | DBS Target(s) Being Studied or that Could Be Considered |
|---|---|---|---|
| Parkinson's disease, essential tremor, and dystonia | Motor | Beta and theta oscillations, GPi overactivity, STN overactivity, and neuronal bursting | STN, GPi, GPe, VL thalamus, PPN, and spinal cord |
| Major depression | Limbic | Increased activity in OFC, SCC, amygdala, and VS, failure to downregulate amygdalar activation | SCC, NAcc, habenula, and medial forebrain bundle |
| Obsessive-compulsive disorder | Motor/limbic | OFC hyperactivity and failure of VS-mediated thalamofrontal inhibition | NAcc, ITP, ALIC, and STN |
| Tinnitus | Auditory | Sensory deafferentation, thalamocortical dysrytmia | Auditory pathways |
| Tourette's syndrome | Motor/limbic | Overactive direct pathway, failure of thalamocortical inhibition | GPi and CM-Pf |
| Schizophrenia—positive symptoms | Executive function, cognitive, and reward | Thalamocortical dysrhythmia, failure of saliency networks | Temporal cortex and NAcc |
| Schizophrenia—negative symptoms | Motivation, reward, cognitive, and mood | Mesolimbic/mesocortical dysfunction, failure to engage anticipatory hedonic system | NAcc, VTA, and SCC |
| Alzheimer's disease | Cognitive and memory circuits | Beta amyloid plaques throughout the brain, DMN dysfunction, cholinergic degeneration, and entorrhinal cortex and hippocampal atrophy | Fornix, entorhinal cortex, hippocampus, cingulate, precuneus, frontal cortex, and nucleus basalis |
| Pain (phantom pain, deafferentation pain, central pain, and nociceptive pain) | Sensory systems and interoceptive awareness | Sensory deafferentation and abnormal neuronal spontaneous bursting behavior | Sensory pathways, periventricular/ periaqueductal areas, and cingulate insula |
| Addiction | Reward | NAcc sensitivity to reward | NAcc |
| Anorexia nervosa | Reward and mood | Frontoparietal disconnection, parietal hypometabolism, insular abnormality, and SCC overactivity | SCC and NAcc |
| Epilepsy | Various | Abnormal excitability and synchrony | CM thalamus, anterior thalamic nucleus, thalamus, and seizure focus |

GPi, globus pallidus internus; GPe, globus pallidus externus; VL, ventrolateral; OFC, orbitofrontal cortex; VS, ventral striatum; NAcc, nucleus accumbens; DLPFC, dorsolateral prefrontal cortex; ITP, inferior thalamic peduncle; ALIC, anterior limb of internal capsule; CM-Pf: centromedian-parafascicular; VTA, ventral tegmental area; DMN, default mode network; STN, subthalamic nucleus; PPN, pedunculopontine nucleus; SCC, subcallosal cingulate.

synchrony with 4–8 Hz oscillatory behavior leads to tremor, while oscillation in the beta band (15–30 Hz) may be responsible for akinesia (Kühn et al., 2008; Little and Brown, 2012). Inhibition of the locomotor pedunculopontine nucleus (PPN) region in the brainstem through overactive descending inhibitory GABAergic axons from the internal segment of the globus pallidus may contribute to gait disturbances (Pereira et al., 2008; Thevathasan et al., 2012; Hamani et al., 2011a). Disturbances in the appropriate selection of motor programs and loss of center-surround inhibition may contribute to the cocontraction of muscles that may contribute to slowness and rigidity (Mink, 1996). Of the major symptoms, however, the pathophysiology of rigidity is perhaps the least well understood.

DBS is being applied to different nodes of the motor circuit for different features of PD (Figure 3A). GPi and STN are typically selected for patients with prominent rigidity, akinesia, tremor, motor fluctuations, and dopamine-related involuntary movements. DBS in these structures has been found to produce significant and long-lasting benefits (Castrioto et al., 2011; Oyama et al., 2012). Patients suffering from tremor-dominant PD typically undergo thalamotomy or DBS of the ventral intermediate nucleus (Vim) of the thalamus, the same target used in patients with essential tremor (ET) (Savica et al., 2011). While the STN and GPi DBS targets are perhaps similarly effective treating the major motor manifestations, neither provides sufficient and enduring benefit for the gait and postural disturbances seen in PD. The PPN, a brainstem structure critical for posture and gait that receives both basal ganglia and spinal cord feedback, is a newer potential target selected in patients with postural instability and frequent falls (Pahapill and Lozano, 2000; Pereira et al., 2008, 2011; Benabid and Torres, 2012). Early reports suggest that unilateral PPN stimulation in PD patients with gait disturbances can lead to less falling and greater postural stability (Stefani et al., 2007; Ballanger et al., 2009; Wilcox et al., 2011). Functional imaging studies show that PPN DBS results in strong activation of the intralaminar thalamic nuclei and the cerebellum, providing clues to the possible mechanism of action of stimulation in this region (Ballanger et al., 2009).

Modulating motor circuits with DBS in PD patients has yielded significant benefit, but there remain several questions currently

under active investigation. It is not yet clear, for example, how the clinical benefit with DBS is achieved, and why some symptoms (e.g., tremor) respond more quickly than others (e.g., gait and postural disturbances). Further, although efforts are being made to individualize targeting and stimulation parameters, it is unclear what the optimal stimulation settings should be for each patient, and this remains at present somewhat burdensome and, to a certain extent, an "art" as well as a science. Facilitation of stimulation parameter testing and selection could be potentially improved in a number of ways including through careful imaging detailing the exact position of electrode contacts in the brain, modeling the spread of the electrical current fields (McIntyre et al., 2004), the identification of physiological changes with stimulation that are predictive of long-term benefit, and the development of more automated algorithms to optimize stimulation settings.

Unfortunately, with time and disease progression, the majority of PD patients develop a number of symptoms, including speech, gait, and cognitive impairment, that are largely resistant to currently available medications and DBS surgery (Hely et al., 1999, 2005). More research is needed to elucidate the pathogenesis of these nonmotor and dopamine-resistant symptoms of PD and the potential impact of DBS on them. There is an increased awareness that the neural substrates mediating the major motor manifestations are separate and distinct from those responsible for the psychiatric and cognitive disturbances. Indeed for multisymptomatic disorders such as PD, the concept of multifocal DBS targeting, for example, implanting stimulating electrodes in both a motor and a cognitive node, is starting to emerge (Aarsland et al., 2012; Uitti, 2012).

DBS of the Vim nucleus of the thalamus is also well established to treat patients with ET, producing important and long-lasting reductions in tremor and improvements in quality of life (Hubble et al., 1996; Koller et al., 2001). There are a number of intriguing observations in ET patients including the delayed loss of benefit of DBS in some patients (Kumar et al., 2003). Further, and perhaps more perplexing, is the observation in a small number of patients that after an extensive period of stimulation, they obtain seemingly permanent suppression of their contralateral arm tremor without requiring ongoing stimulation (Kumar et al., 2003). The explanation for this curious finding is uncertain, but this could be related to changes in neural activity as a consequence of prolonged stimulation or a progressive DBS-induced lesion producing, in effect, a "therapeutic" thalamotomy lesion. Long-term post mortem studies in patients receiving DBS, however, suggest that stimulation produces little overt reaction in the neuropil, and there is no evidence for progressive lesions with prolonged stimulation (Haberler et al., 2000).

DBS is also being used to treat a number of other movement disorders including primary and secondary dystonia, a variety of other tremor disorders such as multiple sclerosis-associated tremor (Brice and McLellan, 1980) or tremor after stroke or head injury (Lyons and Pahwa, 2008), and neurodegenerative diseases with associated movement disorders including Huntington's disease (Moro et al., 2004; Kang et al., 2011), pantothenate kinase-associated neurodegeneration (PKAN) (Castelnau et al., 2005; Mikati et al., 2009), X-linked dystonia or Lubag (Evidente et al., 2007; Wadia et al., 2010), fragile X (Leehey et al., 2003; Senova et al., 2012), and some spinocerebellar ataxias (Freund et al., 2007). In each of these disorders, various stations along the basal ganglia loop have been targeted with DBS including the thalamus, the globus pallidus, the subthalamic nucleus and their associated afferent, and efferent projections with variable clinical benefit (Figure 3A).

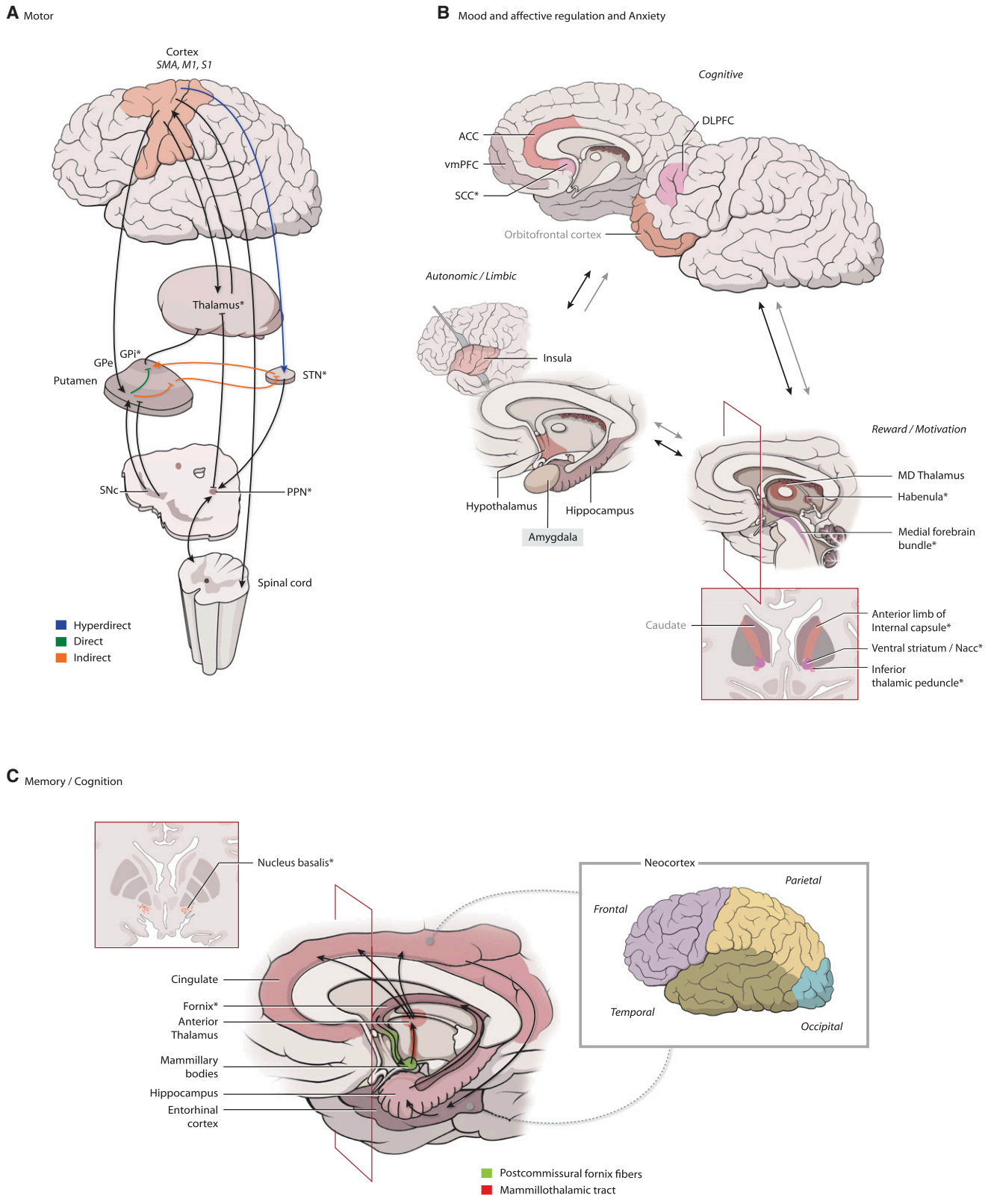
Of these movement disorders, the FDA has granted Humanitarian Device Exemption, and there is the most information for DBS in dystonia. Dystonia is characterized by involuntary muscle contractions that cause slow repetitive movements or abnormal postures. The evidence for pathological activity in dystonia is accumulating and includes abnormalities in network functioning discovered by functional imaging, local field potentials, and evidence of abnormal activity and maladaptive plasticity in cortical and subcortical areas and individual neurons (Ceballos-Baumann et al., 1997; Lenz et al., 1999; Silberstein et al., 2003; Asanuma et al., 2005; Carbon et al., 2010). The benefits of DBS can be particularly striking in patients with primary dystonia (Kumar et al., 1999; Vidailhet et al., 2005; Isaias et al., 2009; Haridas et al., 2011). In many of these patients, in contrast to DBS for PD, improvements are delayed by days to weeks and progress over time. The mechanism responsible for variable time course of these responses are not well understood but could include the need for changes in musculoskeletal function, the process of motor relearning after a prolonged period of motor disuse or dysfunction, or reflect the temporal profile of the underlying plastic changes in circuit organization or efficacy that have occurred as a consequence of stimulation. Equally interesting is that in some patients, dystonic symptoms can return almost immediately upon stimulation cessation, while in others the clinical benefits last days or weeks (Cif et al., 2012; Stavrinou et al., 2012).

## DBS for Psychiatric Disorders

The success of DBS in treating movement disorders has served at an impetus to revisit neurosurgery for psychiatric disease. The reversibility and adaptability of DBS increase its appeal and its acceptance over lesion surgery, particularly in this group of patients with increased vulnerability. Significant challenges arise when applying DBS to psychiatric disorders, however, including the scarcity of predictive animal models, the incomplete understanding of the neuroanatomical substrates generating symptoms, the missing information on connectivity and network properties, and the ethical challenges in conducting clinical trials in psychiatric patient populations (Rabins et al., 2009; Schlaepfer and Fins, 2010; Fins et al., 2011a; Lipsman et al., 2012). While DBS is being studied in a number of psychiatric conditions, including addiction (Kuhn et al., 2011), eating disorders (Lipsman et al., 2013), and Tourette's syndrome (Vandewalle et al., 1999; Porta et al., 2012), here we focus on two major disorders: major depression and OCD.

## Major Depressive Disorder and Mood Circuits

MDD is the most common psychiatric condition, with a lifetime prevalence of 16% (Kessler et al., 2003). Several theories related to the psychological, social, biological, and biochemical underpinnings of depression have been proposed, and treatments are typically aimed at ameliorating these specific disturbances

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(Keitner and Mansfield, 2012). Although a significant portion of patients benefit from these approaches, a substantial number, up to 35%, do not and are deemed to have treatment-resistant depression (Kennedy et al., 2001; Kupfer et al., 2012). As in PD, surgical treatments, ranging from ablation to noninvasive transcranial stimulation and DBS, have evolved to manage patients with treatment-resistant MDD for whom conventional therapy has failed (see Holtzheimer et al., 2012 for review). Here, too, an improved understanding of the neural circuitry of mood has led to hypothesis-driven targets for DBS intervention that mirror the major symptoms of the illness (Figure 3B).

MDD is a multifaceted illness. The clinical picture can include symptoms affecting motor and vegetative function (psychomotor retardation or agitation, sleep, and appetite), mood and cognition (affect, attention, and concentration), perceptual (guilt, biases, and judgments), and reward (anhedonia) systems. With this diverse constellation of symptoms crossing multiple domains, it seems unlikely that the illness can be ascribed to dysfunction of a single anatomic structure, circuit, neurotransmitter system, or gene. It has also become clear that MDD involves a complex biological-environmental interaction that requires a multilayered approach to treatment (Keitner and Mansfield, 2012). Because the diversity of symptoms is greater, the animal models are less informative, and the pathophysiology less well known, and perhaps because the function of the cortical components of the putatively dysfunctional circuits is less well understood, mood disorders are more complex to model and understand than motor disorders.

Functional neuroimaging is a strong driver of progress in psychiatric disease. It does this by revealing the location of dysfunctional brain areas, giving insights into the nature of the physiological disturbance, and identifying new potential targets for intervention, all of which can lead to hypotheses-driven approaches to experimental DBS therapeutics. Such studies test whether the functional abnormalities observed in patients can be recalibrated or reversed with stimulation and whether the induced changes can be correlated with clinical improvement. One specific example of this principle is the identification of the subcallosal cingulate area, a brain region activated by the induction of sadness, which is hypermetabolic in MDD patients compared to healthy age-matched controls (Mayberg, 1997; Damasio et al., 2000; Mayberg et al., 2005). This was the first potential DBS target for psychiatric disease tested on the basis of functional imaging.

Identifying the neuroanatomical substrates mediating the clinical manifestations of MDD across cognitive, affective, reward/motivation, and limbic domains poses a challenge with treatments having to address the dysfunction across these multiple brain areas (Figure 3B) (Anderson et al., 2012). Intervention in the subcallosal cingulate region, for example, a hub where several white matter pathways converge, could theoretically influence several depression domains: reward dysfunction through projections to nucleus accumbens, cognitive dysfunction through reciprocal projections to frontal cortical regions, and autonomic/vegetative dysfunction through primary hypothalamic, insular, and amygdalar connections (Figure 3B).

In parallel with the circuits becoming better characterized, the nature of the dysfunction within these circuits in MDD is also currently an area of active investigation, but much work remains (Tables 1 and 2). Various observations have been made, ranging from focal atrophy and volumetric losses in, for example, the hippocampus and the subcallosal area to dysfunctional metabolic activity as well as neurochemical and neurophysiologic deficits at the single-neuron to neuronal ensemble level (Price and Drevets, 2012; Palazidou, 2012; Broadway et al., 2012). To date, there are few studies examining single-unit or local field potentials in prominent mood circuit structures. Studies have explored decision-making conflicts as well as reward-associated behavior in conjunction with neuronal recordings from anterior and midcingulate, as well as reward-circuit structures (Cohen et al., 2009; Sheth et al., 2012). This is an area that is ripe for further exploration and that will shed more light on the underlying mechanisms of circuit dysfunction in MDD. Such research may help also predict which patients are more likely to respond to DBS or help to personalize the choice of therapeutic target for each patient. In one recent example, neurophysiologic studies that have combined SCC DBS in MDD with electroencephalogram pre- and postoperatively found that pretreatment (baseline) alpha-theta concordance predicted response to DBS treatment (Broadway et al., 2012).

Currently, all DBS targets for depression are investigational, and these include the subcallosal cingulate (SCC), nucleus accumbens/ventral striatum (NAcc/VS), inferior thalamic peduncle (ITP), the medial forebrain bundle (MFB), and habenula

**Figure 3. Circuit Diagrams and DBS Targets for Motor, Mood, Anxiety, and Cognitive Pathways**

Diagrams shown are simplified schematics with not all possible, or known, connections shown. Circuitopathies affecting these pathways result in clinical disorders, such as Parkinson's disease, major depression, obsessive-compulsive disorder, and Alzheimer's disease. DBS at areas with an asterisk are in current use or evaluation. Only thalamic, GPi, and STN DBS targets are currently approved for PD. Other targets and disorders are investigational.

(A) Direct, indirect, and hyperdirect pathways through the basal ganglia, with projections back to the neocortex.

(B) The heterogeneous clinical picture of major depression is probably governed by reciprocal projections between typically frontal cortical structures, governing cognitive functions ("top-down"), striatal and basal ganglia structures influencing reward/motivation, and limbic/autonomic projections influencing vegetative and autonomic features ("bottom-up"). There is also overlap in the circuits governing disordered mood and anxiety. For example, projections from OFC to VS and other components of the limbic basal ganglia, as well reciprocal connections with amygdala and anterior cingulate, are believed to underlie the pathologic anxiety at the core of OCD.

(C) Representation of the main components of the Papez circuit is shown. The fornix represents the principle outflow from hippocampus to limbic structures governing memory and cognition. Neocortical projections from cingulate to components of the default mode network (parietal, temporal, and frontal) feed back to the hippocampal formation. The portion of the fornix beyond the anterior commissure is known as the postcommissural fornix and is shown in green. The projection from the mammillary bodies to the anterior thalamic nucleus is known as the mammillothalamic tract and is shown in red.

OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; vmPFC, ventral medial prefrontal cortex; SCC, subcallosal cingulate; ACC, anterior cingulate cortex; MD, mediodorsal; VS/NAcc, ventral striatum/nucleus accumbens; SMA, supplementary motor area; M1, primary motor area; S1, primary somatosensory area; GPe, globus pallidus externus; PPN, pedunculopontine nucleus; SNc, substantia nigra compacts; SNr, substantia nigra reticulata; GPi, globus pallidus internus.

(Hab) (Figure 3B). Clinical results over the last decade have been promising, providing some relief to patients who have failed conventional therapy, including electroconvulsive therapy (ECT). The DBS target for depression with the most data to date is the SCC, initially proposed and piloted in 2005 (Mayberg et al., 2005). PET imaging has shown that DBS applied in the SCC region in MDD patients reverses functional abnormalities including driving down local hyperactivity and modulating remote cortical targets of local and nearby axonal pathways to recalibrate the activity (Mayberg et al., 2005). Follow-up of the first 20 patients showed a 60% response rate (defined as >50% reduction in Hamilton Depression Rating Scale scores) at 6 months postoperatively, with 55% of patients responders at 1 year (Lozano et al., 2008). At 3 years follow-up, response and remission rates were 60% and 50%, respectively (Kennedy et al., 2011). Results from two additional centers corroborated the results of the initial study, with one group reporting 58% and 92% remission and response rates at 2 years and another group 62.5% and 50% at 1 year, respectively (Puigdemont et al., 2011; Holtzheimer et al., 2012). On the other hand, a multicenter study with 21 patients showed much less favorable outcomes with only 29% of patients responding at 1 year (Lozano et al., 2012). The true therapeutic benefits are thus not clearly established or defined and reason for the variability across studies has yet to be determined. Further insights and a more accurate appraisal of the value of DBS of the SCC will require a randomly assigned ''on'' versus ''off'' stimulation-controlled trial. Such a design is currently being studied in a double-blind, crossover, phase III study in which approximately 200 patients with MDD who fulfill entry criteria receive DBS implant and are randomly assigned to receive active or sham stimulation for 6 months, with all patients subsequently receiving active stimulation. Another site, the ventral striatum/nucleus accumbens, a prominent node in the affect and reward circuit, has been proposed as a target of DBS in MDD. One group has reported rates of response of 50% at 1 year, with PET data suggestive of modulation in the broader affective circuit involving the vmPFC and SCC (Bewernick et al., 2010). Reversal of PFC hypometabolism as well as increased metabolism in ventral striatum was found after 1 week of DBS of the nucleus accumbens (Schlaepfer et al., 2008). These results have supported additional trials of NAcc DBS as well as associated structures in the reward-dopaminergic system, including DBS of the medial forebrain bundle. Other targets explored in MDD include the inferior thalamic peduncle and the lateral habenula, both of which have seen promising results but in a very small number of patients (Sartorius et al., 2010; Jiménez et al., 2012; Hoyer et al., 2012). Which DBS targets are best suited for which patients is a central problem to be resolved.

There are several unanswered questions in the DBS for MDD field, many of which are common in other indications. It remains unclear, for example, why some patients appear to respond to DBS while others do not. Heterogeneity of the illness, the lack of a universal definition of ''treatment resistance,'' and individual anatomical variations in neural pathways, network architecture, and function are likely contributory. Patient selection would be helped by specific clinical, neurophysiologic, and/or anatomic predictors of response. In a recent example, SCC overactivity has been suggested as a marker of ultimate response to DBS in MDD (Pizzagalli, 2011). Also puzzling is the observation that the antidepressant effects of DBS is often not immediate but delayed and progressive over a period of 3 to 6 months, suggesting complex, long-latency mechanisms of action. Additional questions relate to optimal stimulation settings, specifically high (greater than 100 Hz) versus low frequency, the necessity of bilateral stimulation, the mechanism of action, and the selection of a single, or multiple, targets to be used in tandem to address different subcircuits and symptoms. Advances in animal models of DBS for depression may help in addressing these issues (Hamani et al., 2010; Hamani and Temel, 2012).

### *Obsessive-Compulsive Disorder and Anxiety Circuits*

OCD, with a prevalence of 1%–3%, is among the most common anxiety disorders (Bourne et al., 2012). Its clinical heterogeneity and high levels of treatment resistance also make it a challenging condition to treat. OCD includes both a cognitive component, with persistent anxiety-generating obsessions (e.g., cleanliness), as well as a motor component, with time-consuming and disabling compulsions (e.g., washing). The most effective treatments to date involve a combination of serotonin reuptake inhibition and psychotherapy (McGuire et al., 2012). Unfortunately, as in MDD, a substantial proportion of patients remain symptomatic despite optimization of treatment.

Neuroimaging studies have helped elucidate the neural circuitry of OCD, supporting a model of network dysfunction wherein frontal cortical structures, such as those involved in decision making, project to, and receive feedback from, corresponding basal ganglia nuclei involved in reward and action selection pathways (Bourne et al., 2012) (Figure 3B). Importantly, structures outside of the traditional CSTC circuit have been implicated in a more extensive network including the anterior cingulate and amygdala, highlighting the challenges of attributing OCD symptoms to a single dysfunctional circuit (Milad and Rauch, 2012). Consistently implicated structures include the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and caudate, which show metabolic differences compared to controls, both at rest and in response to provocative stimuli (Swedo et al., 1992; Perani et al., 1995; Saxena et al., 1999, 2004). The involvement of basal ganglia structures in OCD underscores its unique place among the anxiety disorders and may be a clue about its underlying pathogenesis. For example, OCD is frequently comorbid with neuropsychiatric conditions such as Tourette's syndrome, and OCD-type behaviors are prevalent in patients with striatal and basal ganglia pathology (Cummings and Frankel, 1985; Laplane et al., 1989; Maia et al., 2008). Although OFC hyperactivity is among the most reliable associated findings in OCD patients, it remains unclear how structural and functional changes in OFC and its projections translate into OCD symptoms. Also undetermined is whether activity detected in any structure is the cause of ongoing obsessions or the consequence of an attempt to suppress unwanted thoughts and behaviors (Maia et al., 2008). Notwithstanding, converging evidence points to a relatively parsimonious collection of structures whose dysfunction, whether locally or as a result of up- or downstream effects, is associated with OCD symptoms. Several of these structures have been the targets of DBS therapy, and a number of studies have been

completed or are ongoing. Targets of DBS intervention for OCD to date include the STN, anterior limb of the internal capsule (ALIC), inferior thalamic peduncle (ITP), ventral caudate/striatum (VC/VS), and nucleus accumbens (Greenberg et al., 2006; Okun et al., 2007; Mallet et al., 2008; Jiménez-Ponce et al., 2009; Huff et al., 2010) (Figure 3B). These are in general early studies that involve relatively small numbers of patients. There is no clear indication as to which target may be better suited to which patient or which symptoms. For example, a placebo-controlled, double-blind study of DBS in OCD using the STN target found a 31% decrease in Yale-Brown Obsessive Compulsive Scale (YBOCS) score between active and sham stimulation groups (Mallet et al., 2008). Using a modified definition of treatment response (>25% reduction in YBOCS), this group reported 12/16 patients responded to stimulation at follow-up. A more stringent definition of response (>35% reduction in YBOCS) was used in other studies exploring additional DBS targets, in which rates of response in open label studies were 66.7% for ventral striatum/capsule (Goodman et al., 2010) and 56% for nucleus accumbens (Denys et al., 2010). The similar rates of response across these and other targeted structures along the orbitofrontal-striato-thalamic loop could suggest common effects of DBS and perhaps similar circuitry being influenced (Jiménez-Ponce et al., 2009).

The clinical manifestations of OCD are heterogeneous. Some patients are, for example, hoarders and others are checkers, and the neural substrates for the various symptoms are beginning to be understood and localized (Mataix-Cols et al., 2004; An et al., 2009). This heterogeneity contributes to the complexity of treating this disorder and several important questions remain. It is unclear, as in MDD, whether all patients with OCD should receive the same procedure, or whether a tailored DBS approach is required for different subcategories of illness. There is an important need for more functional imaging studies and animal models of DBS in order to help elucidate pathways and mechanisms in OCD and other psychiatric disorders (Hamani and Temel, 2012).

### *Alzheimer's Disease and Memory/Cognitive Circuits*

Over 5 million people in North America have AD. The progressive disorder is characterized by various pathological processes including regionally specific and sequential brain atrophy, amyloid deposition, intraneuronal neurofibrillary tangles, and synaptic loss (Ballard et al., 2011). Through mechanisms that are incompletely understood, these processes lead to widespread network dysfunction including deficits in function of the default mode network of the brain and the progressive decline in glucose utilization in specific brain areas as the disease advances (Herholz et al., 2007; Ballard et al., 2011; Jones et al., 2011; Schwindt et al., 2012). Treatments in current use act by increasing cholinergic or antagonizing glutaminergic transmission (Massoud and Léger, 2011). These measures are only mildly and temporarily beneficial. More effective therapies are clearly needed.

Two new approaches using DBS in Alzheimer's disease are currently being examined. In one approach, first attempted in 1985, DBS is being applied to the nucleus basalis of Meynert to modulate cholinergic function (Turnbull et al., 1985) (Figure 3C). This approach is based on the notion that increasing cholinergic tone, the same mechanism of action as the acetylcholinesterase inhibitors in the principle class of drugs used in AD, could produce improvements in cognitive function. DBS of the nucleus basalis is currently in phase I clinical trials and there are no publications to date. The second approach involves DBS of the circuit of Papez, a series of interconnected brain areas important in the control of memory (Figure 3C). In a small phase I clinical trial, DBS was used to drive activity within memory and cognitive circuits by stimulating the fornix of six patients with AD (Laxton et al., 2010). This approach considers AD from the standpoint of being a circuit disorder in which localized dysfunction arising secondarily to AD pathology has long-reaching consequences transmitted across an extensive brain network. To date, the investigators have shown that fornix DBS drives activity transynaptically across the circuit of Papez and the default mode network (Laxton et al., 2010). In addition, they have shown that the progressive decline in glucose utilization in temporal and parietal brain areas that is characteristic in AD can be slowed down or partially reversed (Smith et al., 2012). These observations suggest that the network dysfunction in AD may arise, at least in part, as a consequence of impaired synaptic inputs or activity to deafferented regions, particularly temporal and parietal areas of the cortex. DBS may be able to modulate these dysfunctional circuits and change the pattern and level of synaptic output leading to an augmentation in the activity of cortical areas within the network. The implication is that at least a portion of the dysfunction of cerebral cortical areas in AD may be reversible and, by extension, that restoring activity in the cortical fields could be accompanied by an amelioration of cognitive decline or a return of memory and cognitive function. Of interest, recent observations in patients with epilepsy have shown that entorhinal stimulation may enhance certain aspects of memory (Suthana et al., 2012). This suggests that this node in the memory/cognitive circuit could also be considered for patients with AD and other cognitive disorders.

The early experiments of stimulation within the circuit of Papez are being informed by concurrent studies in experimental animals. Using the homologous targets and stimulation parameters used in AD patients, DBS in rodents at various nodes across this circuit including the anterior nucleus of the thalamus (Hamani et al., 2011b) and the entorhinal cortex (Stone et al., 2011b) and fornix (Hescham et al., 2012) is having a number of behavioral effects including improving performance on delayed nonmatching to sample tasks and enhancing spatial memory in normal animals. An unexpected finding is that DBS within these circuits drives neurogenesis 2- to 3-fold in the subgranular zone of the hippocampus in mice and rats (Toda et al., 2008; Stone et al., 2011b). The DBS-induced newly born granule cells appear to have normal morphology and become physiologically active, expressing c-*fos* after behavioral testing, suggesting that they are capable of being integrated in functional circuits (Stone et al., 2011a). That the improvements in memory that occur with DBS are delayed by weeks and can be blocked by antimitotic agents is consistent with the notion that the augmented memory is dependent on neurogenesis. While adult humans are known to have the capacity for hippocampal neurogenesis (Eriksson et al., 1998), whether neurogenesis is induced by DBS in patients and whether this phenomenon contributes in any way to the clinical effects are questions that for the time being remain unanswered.

**Table 3. Proposed Mechanisms of Action of DBS**

| Mechanism | Example Evidence |
|---|---|
| DBS inhibits the activity of target neurons | |
| Depolarization blockade (K, Na effects) | Reduction of GPi activity with GPi stimulation (Wu et al., 2001; Dostrovsky et al., 2000); firing suppression in STN neurons after STN stimulation (Toleikis et al., 2012); DBS associated with increased ATP and activation of adenosine A1 receptors (Bekar et al., 2008); frequency-dependent modulation of synaptic function/neurotransmission (Contreras and Llinas, 2001) |
| Synaptic failure | |
| Neurotransmitter depletion (glutamate) | |
| Hyperpolarization of neuronal cell bodies and dendrites | |
| Release of inhibitory neurotransmitter (GABA; adenosine) | |
| Synaptic inhibition of afferent projections | |
| DBS activates target neurons | |
| Increased glutamate in efferent projection targets | Decreased VL thalamus activity with GPi stimulation (activation of pallidothalamic pathways) (Montgomery, 2006; Montgomery and Gale, 2008; Anderson et al., 2003); increased GPi activity with STN stimulation (Hashimoto et al., 2003); increased neurotransmitter and second messenger release in downstream structures of DBS target (Benazzouz and Hallett, 2000; Stefani et al., 2005); STN DBS leads to increase in DA breakdown products (HVA) and increased SNc neuron firing rates (Walker et al., 2009; Lee et al., 2004) |
| Increased dopamine in remaining SNc neurons in PD | |
| DBS both excites and inhibits target neurons | |
| Decoupling of soma and axons (inhibition of soma, activation of axons) (antidromic, orthodromic) | Computational models showing driving of axonal output by stimulation independent of activity on neuronal cell body (McIntyre et al., 2004); STN DBS leads to LTP and LTD in rat STN neurons (Shen et al., 2003); stimulation leads to plasticity of SNpr neurons in patients with PD (Prescott et al., 2009) |
| Plasticity (long-term potentiation [LTP], long-term depression [LTD]) | |
| DBS disrupts pathologic oscillatory patterns and generates an "information lesion" | |
| Replacement of irregular bursting cells with regular high-frequency firing | STN DBS and dopaminergic medication reduce beta-band oscillations in PD (Doyle et al., 2005; Little and Brown, 2012); DBS disrupts and overrides network-wide pathologic activity (McIntyre and Hahn, 2010) |
| Promotion of "prokinetic" frequencies and abolition of pathologic beta-band frequencies | |
| Produces/generates "jamming" signal | |
| DBS has trophic effects, leads to neurotrophin release, and generates new neurons (neurogenesis) | Entorhinal cortex stimulation leads to new DG cells that are functionally incorporated into memory circuits (Stone et al., 2011a, 2011b) |

GABA, gamma-aminobutyric acid; ATP, adenosine triphosphate; SNc, substantia nigra compacta; HVA, homovanillic acid; STN, subthalamic nucleus; VL, ventrolateral; DA, dopamine; SNpr, substantia nigra pars reticulata; DG, dentate gyrus.

There is currently an active phase II clinical trial of DBS using sham versus active stimulation-controlled arms to test the potential safety and clinical benefits of this approach in patients suffering with AD.

## Mechanisms and Kinetics of DBS

One of the most controversial aspects of DBS is its proposed mechanism of action and this remains an area of intense investigation (Kringelbach et al., 2010). This issue has several facets including (1) how neural structures generally communicate with each other on a subcellular, neuronal, and fiber-pathway level; (2) the types of dysfunction that occur in neural circuit disorders and how these are affected by neuromodulation; and (3) the plastic changes that occur in the brain as a consequence of stimulation.

It is clear from the clinical and functional imaging literature that focal stimulation has local and remote effects across brain networks. What is not yet clear is how this influence is achieved (Table 3). Theories abound and, despite a lack of consensus, it appears that the initial simplistic view that DBS was merely producing a physiological block or reversible lesion, based largely on what can be similar clinical effects of lesioning and stimulation, is not entirely correct. New models emphasize that DBS can act by "jamming" pathological activity in networks and seek to define the nature and mechanism of how stimulation disrupts pathological activity (McIntyre and Hahn, 2010). Further, while the majority of data have supported the view that DBS produces a functional lesion, a number of recent observations suggests that DBS works by driving activity. Stimulation of axonal pathways in the brain produces a clear positive response, for example, motor contraction with stimulation of corticospinal fibers within the internal capsule and the perception of phosphenes with stimulation of the optic tract, provide unequivocal evidence that stimulation is activating these pathways. DBS experiments showing the synaptic release of neurotransmitters at distal axonal projections as measured by microdialysis (Windels et al., 2005) or the physiological effects of DBS at downstream neuronal targets are consistent with the notion that DBS activates the output of the stimulated target with the ultimate effect on the postsynaptic neurons, depending on whether the stimulated projection is predominantly excitatory or inhibitory (Dostrovsky et al., 2000; Hashimoto et al., 2003;

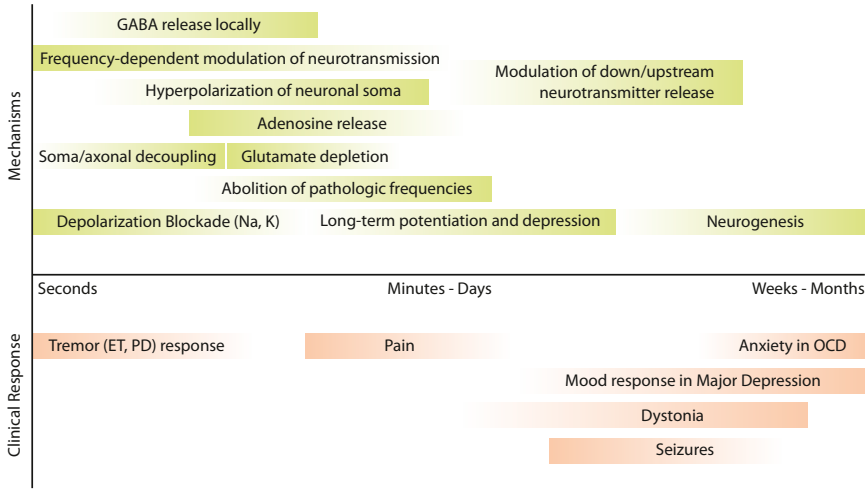


**Figure 4. Kinetics of DBS Response**
Mechanisms of action for DBS can be divided according to the neural elements being affected and the time course of the response. Some clinical symptoms, such as tremor, respond much more quickly than other symptoms, such as anxiety, depression, and dystonia. This may reflect differences at the microenvironment level immediately surrounding the DBS electrode and/or more remote neural components that lie up- or downstream.
GABA, gamma-aminobutyric acid; ET, essential tremor; PD, Parkinson's disease; OCD, obsessive-compulsive disorder.

Windels et al., 2005; Vitek et al., 2012). In addition, potentially opposing mechanisms and separate loci of action can be engaged simultaneously. Indeed, one prominent model has DBS doing both excitation and inhibition, whereby the soma and axon are electrically decoupled by DBS, leading to somatic inhibition and muting of afferents, as well as to axonal excitation and activation of efferents (McIntyre et al., 2004). Such a model is appealing as it provides a parsimonious explanation for the neurophysiologic findings of downstream activation and intrastructural inhibition (Johnson et al., 2008).

The seemingly contradictory findings and the challenges in studying DBS mechanisms arise as a consequence of a large number of experimental variables including the numerous approaches (imaging, neurophysiology, microdialysis, and behavioral readouts), the specific neural elements being studied, which molecules are released with stimulation (neurotransmitters, ions, and neurotrophins), the local synaptic arrangements, the nature and mode of stimulation, the current densities that vary with physical features of the electrodes being used, and, importantly, the varied latencies (short versus long term) of the observed effects. The clinical effects are the algebraic sum of these various elements, some of which trend in the same direction, others of which operate at cross-purposes.

An important step in understanding the mechanism of action of DBS is establishing what neural elements in the brain are excited and determining their relative susceptibility to electrical stimulation. One can consider the effects on neuronal cell bodies, axons, and dendrites with the role of glia being increasingly recognized. Depolarization of an excitable membrane requires flow of electrical charge across that membrane. For a short-duration stimulus generating a steady transmembrane current, the charge transferred is proportional to the product of current and time. Classical teaching (reviewed in Ranck, 1975) informs us that there is a hierarchy of responsiveness of neural elements with, for example, myelinated CNS axons having a chronaxie (a measure of the threshold for excitability) of 50–100 ms activated before cell bodies with a chronaxie in the range of 200–700 ms. In addition, large axons are activated before smaller ones and myelinated axons before unmyelinated ones. Empirical data also indicate that high currents (approximately eight times threshold) in close proximity may block action potentials in axons. The implication is that neural elements in close proximity may be blocked while those a little further away may be stimulated. In addition, it takes less cathodal current than anodal to stimulate a myelinated axon and the orientation of the current in relation to the structure being stimulated is also important, with the voltage gradient parallel to the axons being most effective. These concepts are being incorporated in the emerging area of modeling current flow from the electrodes to the brain environment where they are placed (McIntyre et al., 2004). Such an approach will be useful in helping to select stimulus parameters from a vast number of possible combinations to optimize clinical benefits and limit stimulation-related adverse effects. This may also help drive innovative strategies involving electrode design and new modes of stimulation, for example, varying wave forms to steer current and provide selectivity for neural elements are to be preferentially activated or avoided.

The effects of DBS on the local microenvironment are also being increasingly recognized. Release and/or accumulation of neurotransmitters or ionic elements from either neurons or glia including, for example, adenosine, can help explain short-term changes or lesional-like effects of stimulation but may be difficult to reconcile with some of the observed long-term changes and the long latency of clinical responses (Lee et al., 2004; Bekar et al., 2008; Shon et al., 2010; Chang et al., 2012).

The "ON" and "OFF" kinetics of the clinical effects of DBS are proving to be at once complex and informative, especially in discussions surrounding mechanisms of action and response (Figure 4). While some of the effects of DBS are immediate, such as the cessation of tremor with the application of thalamic stimulation, others, including the improvements seen in dystonia, depression, and epilepsy, can be delayed and progressive, taking weeks or months of stimulation to achieve maximal clinical benefit. In several disorders, the short or long latency of the effect is often mirrored by the variable duration of the washout of the clinical effects. The return of PD tremor when the stimulation is turned off, for example, occurs nearly immediately, while there can be ongoing improvements for days to weeks after the cessation of stimulation in cases of DBS for depression, epilepsy, or dystonia. Multiple mechanisms each with corresponding kinetics are likely at play. For example,

**Table 4. Ethical Considerations in DBS Practice and Research**

| Considerations | Example Questions |
|---|---|
| Patient selection | How should "treatment resistance" for DBS-eligible conditions be defined (Schermer, 2011; Lipsman et al., 2010b)? |
| | Should DBS be considered a treatment of "last resort" (Juckel et al., 2009)? |
| | What are the criteria for the development of DBS trials for novel indications, and how can these be empirically defined (Lipsman et al., 2010a)? |
| Informed consent | Do patients understand the difference between research trials and treatment (therapeutic misconception) (Fisher et al., 2012)? |
| | Do patients with refractory neuropsychiatric conditions have the capacity to consent and, if not, is proxy consent by a caregiver or guardian sufficient (Lipsman et al., 2012)? |
| Governance | What measures need to be in place for oversight and regulation of individuals and centers performing DBS? |
| Resource allocation | Does the availability of DBS only in high-volume, expert centers violate the ethical principle of justice, and how can access to experimental procedures and treatment be optimized (Bell et al., 2011)? |
| Defining outcomes | What is the impact of DBS on personality and personhood (Schermer, 2011; Lipsman and Glannon, 2012; Gilbert, 2012)? |
| Special populations | What considerations need to be in place to manage vulnerable or desperate patients, as well as children with DBS (Rabins et al., 2009)? |
| Responsible publishing | How should results of DBS trials in novel and established indications best be communicated to the public (Gilbert and Ovadia, 2011)? |
| | Do case reports have a place in the DBS literature and should these, along with results of larger trials, be submitted to a formal registry (Schlaepfer and Fins, 2010)? |
| Conflicts of interest | What is the best way to manage the relationship between clinician researchers and the DBS industry (Fins and Schiff, 2010; Fins et al., 2011b)? |
| Enhancement | Should DBS, or other forms of neuromodulation technology, be used in otherwise healthy individuals to enhance "normal" function (Mendelsohn et al., 2010; Lipsman et al., 2011)? |

SCC DBS for MDD is often accompanied by an intraoperative "acute stimulation" effect marked by transient improved mood and increased engagement and motivation that occurs within seconds of electrode testing. This stands in contrast to the approximately 2–3 months that are often required to see maximal clinical benefit on depression with chronic stimulation. Activation of local elements, release of neurotransmitters, alterations of cerebral blood flow, and autonomic influences may explain the acute effects, but other mechanisms are required to account for the more long-term effects.

The lasting changes in the behavior of neural circuits as a consequence of DBS, as is characteristic of neuroplasticity, are becoming increasingly recognized. Although their mechanisms are not well understood, they could involve a variety of processes, including changes in synaptic efficacy, long-term potentiation and depression, trophic factor release, changes in connectivity, and the possible induction of neurogenesis (Figure 4 and Table 3). The time course of the changes occurring over months could be explained by new pathways being structurally modified or created and/or alternative neural pathways being recruited or reinforced. As described above, preclinical models employing DBS of the anterior thalamic nucleus or entorhinal cortex in rodent models found significant increased neurogenesis with new neurons functionally incorporated into established memory circuits (Toda et al., 2008; Stone et al., 2011b). Pathologic studies, as well as neuroimaging investigations (Manganas et al., 2007) before and after DBS, will help elucidate whether this phenomenon occurs in human patients as well.

## Future Directions in Neuromodulation Research

Interest in DBS is growing at an exponential rate and its profound effects are introducing a number of complex issues and raising several important and interesting ethical questions (Table 4). This is prominently at issue in novel, particularly neuropsychiatric, indications and in the context of investigational studies, in which the perceived benefits to the patient and society need to be weighed against possible risks, and safeguards must be put in place to ensure the proper use of these technologies in patients that may be cognitively or judgmentally impaired. Here, the involvement of a multidisciplinary team with domain expertise in the condition of interest is critical to aiding patient selection and facilitating postoperative follow-up (see Rabins et al., 2009 and Lipsman et al., 2010a for review of other ethical issues in DBS research). So that the abuses of neurosurgery for psychiatric conditions of the early days are not repeated, it is imperative that research teams engaged in DBS for both established and emerging indications be mindful of these ethical challenges and heed the ethical principles of beneficence and nonmaleficence at every stage of DBS practice, from patient selection to dissemination of results.

In the years to come, the field of DBS will see improvements and evolution. Neuromodulation will remain a critical scientific and clinical tool and we predict that the field will continue to grow, bringing greater clinical benefits and being applied to more patients. There will be technological advances, for example, better electronics, current steering, parameter optimization algorithms, stimulation delivery that is responsive to physiological inputs, and the advent of wireless systems to allow real-time export and analysis of physiologic data captured from implanted electrodes. Developments in optogenetics and nanotechnology, utilizing light- and temperature-sensitive channels, respectively, will also allow a parsing of subcircuits and modulation of specific pathways, while closed-loop

stimulation systems utilizing physiological or biochemical signal detection and stimulation that adapts to the circumstance will provide more tailored and individualized therapy. Further, newer, less invasive methods, including focused ultrasound and transcranial magnetic and electrical stimulation, will continue to evolve. These innovations will occur in the context of advances in the understanding of neurological and psychiatric disease including better identification of the nature, location, and dynamic properties of brain dysfunction.

The future of DBS will lie at the interface of several disciplines including medical device technology development, structural and functional brain imaging, modeling work, animal experimentation, and experimental human trials. The convergence of technology and biology, coupled with the ongoing unmet clinical need, will drive the development of new brain targets, new clinical indications, and novel methods of neuromodulation.

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## REFERENCES

Aarsland, D., Påhlhagen, S., Ballard, C.G., Ehrt, U., and Svenningsson, P. (2012). Depression in Parkinson disease—epidemiology, mechanisms and management. Nat. Rev. Neurol. *8*, 35–47.

Alexander, G.E., DeLong, M.R., and Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. *9*, 357–381.

An, S.K., Mataix-Cols, D., Lawrence, N.S., Wooderson, S., Giampietro, V., Speckens, A., Brammer, M.J., and Phillips, M.L. (2009). To discard or not to discard: the neural basis of hoarding symptoms in obsessive-compulsive disorder. Mol. Psychiatry *14*, 318–331.

Anderson, M.E., Postupna, N., and Ruffo, M. (2003). Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J. Neurophysiol. *89*, 1150–1160.

Anderson, R.J., Frye, M.A., Abulseoud, O.A., Lee, K.H., McGillivray, J.A., Berk, M., and Tye, S.J. (2012). Deep brain stimulation for treatment-resistant depression: efficacy, safety and mechanisms of action. Neurosci. Biobehav. Rev. *36*, 1920–1933.

Androulidakis, A.G., Brücke, C., Kempf, F., Kupsch, A., Aziz, T., Ashkan, K., Kühn, A.A., and Brown, P. (2008). Amplitude modulation of oscillatory activity in the subthalamic nucleus during movement. Eur. J. Neurosci. *27*, 1277–1284.

Asanuma, K., Ma, Y., Huang, C., Carbon-Correll, M., Edwards, C., Raymond, D., Bressman, S.B., Moeller, J.R., and Eidelberg, D. (2005). The metabolic pathology of dopa-responsive dystonia. Ann. Neurol. *57*, 596–600.

Aziz, T.Z., Peggs, D., Sambrook, M.A., and Crossman, A.R. (1991). Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov. Disord. *6*, 288–292.

Ballanger, B., Lozano, A.M., Moro, E., van Eimeren, T., Hamani, C., Chen, R., Cilia, R., Houle, S., Poon, Y.Y., Lang, A.E., and Strafella, A.P. (2009). Cerebral blood flow changes induced by pedunculopontine nucleus stimulation in patients with advanced Parkinson's disease: a [(15)O] H2O PET study. Hum. Brain Mapp. *30*, 3901–3909.

Ballard, C., Gauthier, S., Corbett, A., Brayne, C., Aarsland, D., and Jones, E. (2011). Alzheimer's disease. Lancet *377*, 1019–1031.

Bechtereva, N.P., Bondartchuk, A.N., Smirnov, V.M., Meliutcheva, L.A., and Shandurina, A.N. (1975). Method of electrostimulation of the deep brain structures in treatment of some chronic diseases. Confin. Neurol. *37*, 136–140.

Bekar, L., Libionka, W., Tian, G.F., Xu, Q., Torres, A., Wang, X., Lovatt, D., Williams, E., Takano, T., Schnermann, J., et al. (2008). Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. Nat. Med. *14*, 75–80.

Bell, E., Maxwell, B., McAndrews, M.P., Sadikot, A., and Racine, E. (2011). Deep brain stimulation and ethics: perspectives from a multisite qualitative study of Canadian neurosurgical centers. World Neurosurg. *76*, 537–547.

Benabid, A.L., and Torres, N. (2012). New targets for DBS. Parkinsonism Relat. Disord. *18*(*Suppl 1*), S21–S23.

Benabid, A.L., Pollak, P., Louveau, A., Henry, S., and de Rougemont, J. (1987). Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl. Neurophysiol. *50*, 344–346.

Benazzouz, A., and Hallett, M. (2000). Mechanism of action of deep brain stimulation. Neurology *55*(12, Suppl 6), S13–S16.

Benazzouz, A., Gross, C., Dupont, J., and Bioulac, B. (1992). MPTP induced hemiparkinsonism in monkeys: behavioral, mechanographic, electromyographic and immunohistochemical studies. Exp. Brain Res. *90*, 116–120.

Bergman, H., Wichmann, T., and DeLong, M.R. (1990). Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science *249*, 1436–1438.

Bewernick, B.H., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., Axmacher, N., Lemke, M., Cooper-Mahkorn, D., Cohen, M.X., et al. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol. Psychiatry *67*, 110–116.

Bishop, M.P., Elder, S.T., and Heath, R.G. (1963). Intracranial self-stimulation in man. Science *140*, 394–396.

Bonelli, R.M., and Cummings, J.L. (2007). Frontal-subcortical circuitry and behavior. Dialogues Clin. Neurosci. *9*, 141–151.

Bourne, S.K., Eckhardt, C.A., Sheth, S.A., and Eskandar, E.N. (2012). Mechanisms of deep brain stimulation for obsessive compulsive disorder: effects upon cells and circuits. Front. Integr. Neurosci. *6*, 29.

Brice, J., and McLellan, L. (1980). Suppression of intention tremor by contingent deep-brain stimulation. Lancet *1*, 1221–1222.

Broadway, J.M., Holtzheimer, P.E., Hilimire, M.R., Parks, N.A., Devylder, J.E., Mayberg, H.S., and Corballis, P.M. (2012). Frontal theta cordance predicts 6-month antidepressant response to subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. Neuropsychopharmacology *37*, 1764–1772.

Brücke, C., Kupsch, A., Schneider, G.H., Hariz, M.I., Nuttin, B., Kopp, U., Kempf, F., Trottenberg, T., Doyle, L., Chen, C.C., et al. (2007). The subthalamic region is activated during valence-related emotional processing in patients with Parkinson's disease. Eur. J. Neurosci. *26*, 767–774.

Carbon, M., Argyelan, M., and Eidelberg, D. (2010). Functional imaging in hereditary dystonia. Eur. J. Neurol. *17*(*Suppl 1*), 58–64.

Castelnau, P., Cif, L., Valente, E.M., Vayssiere, N., Hemm, S., Gannau, A., Digiorgio, A., and Coubes, P. (2005). Pallidal stimulation improves pantothenate kinase-associated neurodegeneration. Ann. Neurol. *57*, 738–741.

Castrioto, A., Lozano, A.M., Poon, Y.Y., Lang, A.E., Fallis, M., and Moro, E. (2011). Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. Arch. Neurol. *68*, 1550–1556.

Ceballos-Baumann, A.O., Sheean, G., Passingham, R.E., Marsden, C.D., and Brooks, D.J. (1997). Botulinum toxin does not reverse the cortical dysfunction associated with writer's cramp. A PET study. Brain *120*, 571–582.

Chang, S.Y., Kim, I., Marsh, M.P., Jang, D.P., Hwang, S.C., Van Gompel, J.J., Goerss, S.J., Kimble, C.J., Bennet, K.E., Garris, P.A., et al. (2012). Wireless fast-scan cyclic voltammetry to monitor adenosine in patients with essential tremor during deep brain stimulation. Mayo Clin. Proc. *87*, 760–765.

Cif, L., Ruge, D., Gonzalez, V., Limousin, P., Vasques, X., Hariz, M.I., Rothwell, J., and Coubes, P. (2012). The influence of deep brain stimulation intensity and duration on symptoms evolution in an OFF stimulation dystonia study. Brain Stimulat. Published online October 8, 2012. http://dx.doi.org/10.1016/j.brs.2012.09.005.

Cohen, M.X., Axmacher, N., Lenartz, D., Elger, C.E., Sturm, V., and Schlaepfer, T.E. (2009). Nuclei accumbens phase synchrony predicts decision-making reversals following negative feedback. J. Neurosci. *29*, 7591–7598.

Contreras, D., and Llinas, R. (2001). Voltage-sensitive dye imaging of neocortical spatiotemporal dynamics to afferent activation frequency. J. Neurosci. *21*, 9403–9413.

Cummings, J.L., and Frankel, M. (1985). Gilles de la Tourette syndrome and the neurological basis of obsessions and compulsions. Biol. Psychiatry *20*, 117–126.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., and Hichwa, R.D. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat. Neurosci. *3*, 1049–1056.

Davis, K.D., Kiss, Z.H., Luo, L., Tasker, R.R., Lozano, A.M., and Dostrovsky, J.O. (1998). Phantom sensations generated by thalamic microstimulation. Nature *391*, 385–387.

Davis, K.D., Taylor, K.S., Hutchison, W.D., Dostrovsky, J.O., McAndrews, M.P., Richter, E.O., and Lozano, A.M. (2005). Human anterior cingulate cortex neurons encode cognitive and emotional demands. J. Neurosci. *25*, 8402–8406.

de Lau, L.M., and Breteler, M.M. (2006). Epidemiology of Parkinson's disease. Lancet Neurol. *5*, 525–535.

Delgado, J.M., and Livingston, R.B. (1948). Some respiratory, vascular and thermal responses to stimulation of orbital surface of frontal lobe. J. Neurophysiol. *11*, 39–55.

Denys, D., Mantione, M., Figee, M., van den Munckhof, P., Koerselman, F., Westenberg, H., Bosch, A., and Schuurman, R. (2010). Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch. Gen. Psychiatry *67*, 1061–1068.

Dickerson, B.C., and Eichenbaum, H. (2010). The episodic memory system: neurocircuitry and disorders. Neuropsychopharmacology *35*, 86–104.

Dostrovsky, J.O., Levy, R., Wu, J.P., Hutchison, W.D., Tasker, R.R., and Lozano, A.M. (2000). Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J. Neurophysiol. *84*, 570–574.

Doyle, L.M., Kühn, A.A., Hariz, M., Kupsch, A., Schneider, G.H., and Brown, P. (2005). Levodopa-induced modulation of subthalamic beta oscillations during self-paced movements in patients with Parkinson's disease. Eur. J. Neurosci. *21*, 1403–1412.

Engelborghs, S., D'Hooge, R., and De Deyn, P.P. (2000). Pathophysiology of epilepsy. Acta Neurol. Belg. *100*, 201–213.

Eriksson, P.S., Perfilieva, E., Björk-Eriksson, T., Alborn, A.M., Nordborg, C., Peterson, D.A., and Gage, F.H. (1998). Neurogenesis in the adult human hippocampus. Nat. Med. *4*, 1313–1317.

Evidente, V.G., Lyons, M.K., Wheeler, M., Hillman, R., Helepolelei, L., Beynen, F., Nolte, D., Müller, U., and Starr, P.A. (2007). First case of X-linked dystonia-parkinsonism ("Lubag") to demonstrate a response to bilateral pallidal stimulation. Mov. Disord. *22*, 1790–1793.

Filion, M., and Tremblay, L. (1991). Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res. *547*, 142–151.

Fins, J.J., and Schiff, N.D. (2010). Conflicts of interest in deep brain stimulation research and the ethics of transparency. J. Clin. Ethics *21*, 125–132.

Fins, J.J., Mayberg, H.S., Nuttin, B., Kubu, C.S., Galert, T., Sturm, V., Stoppenbrink, K., Merkel, R., and Schlaepfer, T.E. (2011a). Misuse of the FDA's humanitarian device exemption in deep brain stimulation for obsessive-compulsive disorder. Health Aff. (Millwood) *30*, 302–311.

Fins, J.J., Schlaepfer, T.E., Nuttin, B., Kubu, C.S., Galert, T., Sturm, V., Merkel, R., and Mayberg, H.S. (2011b). Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation. J. Neural Eng. *8*, 033001.

Fisher, C.E., Dunn, L.B., Christopher, P.P., Holtzheimer, P.E., Leykin, Y., Mayberg, H.S., Lisanby, S.H., and Appelbaum, P.S. (2012). The ethics of research on deep brain stimulation for depression: decisional capacity and therapeutic misconception. Ann. N Y Acad. Sci. *1265*, 69–79.

Follett, K.A., Weaver, F.M., Stern, M., Hur, K., Harris, C.L., Luo, P., Marks, W.J., Jr., Rothlind, J., Sagher, O., Moy, C., et al.; CSP 468 Study Group. (2010). Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N. Engl. J. Med. *362*, 2077–2091.

Freund, H.J., Barnikol, U.B., Nolte, D., Treuer, H., Auburger, G., Tass, P.A., Samii, M., and Sturm, V. (2007). Subthalamic-thalamic DBS in a case with spinocerebellar ataxia type 2 and severe tremor-A unusual clinical benefit. Mov. Disord. *22*, 732–735.

Gilbert, F. (2012). The burden of normality: from 'chronically ill' to 'symptom free'. New ethical challenges for deep brain stimulation postoperative treatment. J. Med. Ethics *38*, 408–412.

Gilbert, F., and Ovadia, D. (2011). Deep brain stimulation in the media: over-optimistic portrayals call for a new strategy involving journalists and scientists in ethical debates. Front. Integr. Neurosci. *5*, 16.

Goodman, W.K., Foote, K.D., Greenberg, B.D., Ricciuti, N., Bauer, R., Ward, H., Shapira, N.A., Wu, S.S., Hill, C.L., Rasmussen, S.A., and Okun, M.S. (2010). Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. Biol. Psychiatry *67*, 535–542.

Greenberg, B.D., Malone, D.A., Friehs, G.M., Rezai, A.R., Kubu, C.S., Malloy, P.F., Salloway, S.P., Okun, M.S., Goodman, W.K., and Rasmussen, S.A. (2006). Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology *31*, 2384–2393.

Greicius, M.D., Srivastava, G., Reiss, A.L., and Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc. Natl. Acad. Sci. USA *101*, 4637–4642.

Haberler, C., Alesch, F., Mazal, P.R., Pilz, P., Jellinger, K., Pinter, M.M., Hainfellner, J.A., and Budka, H. (2000). No tissue damage by chronic deep brain stimulation in Parkinson's disease. Ann. Neurol. *48*, 372–376.

Hamani, C., and Temel, Y. (2012). Deep brain stimulation for psychiatric disease: contributions and validity of animal models. Sci. Transl. Med. *4*, rv8.

Hamani, C., Richter, E., Schwalb, J.M., and Lozano, A.M. (2008). Bilateral subthalamic nucleus stimulation for Parkinson's disease: a systematic review of the clinical literature. Neurosurgery *62*(*Suppl 2*), 863–874.

Hamani, C., Diwan, M., Macedo, C.E., Brandão, M.L., Shumake, J., Gonzalez-Lima, F., Raymond, R., Lozano, A.M., Fletcher, P.J., and Nobrega, J.N. (2010). Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. Biol. Psychiatry *67*, 117–124.

Hamani, C., Moro, E., and Lozano, A.M. (2011a). The pedunculopontine nucleus as a target for deep brain stimulation. J. Neural Transm. *118*, 1461–1468.

Hamani, C., Stone, S.S., Garten, A., Lozano, A.M., and Winocur, G. (2011b). Memory rescue and enhanced neurogenesis following electrical stimulation of the anterior thalamus in rats treated with corticosterone. Exp. Neurol. *232*, 100–104.

Haridas, A., Tagliati, M., Osborn, I., Isaias, I., Gologorsky, Y., Bressman, S.B., Weisz, D., and Alterman, R.L. (2011). Pallidal deep brain stimulation for primary dystonia in children. Neurosurgery *68*, 738–743, discussion 743.

Hariz, M. (2012). Twenty-five years of deep brain stimulation: celebrations and apprehensions. Mov. Disord. *27*, 930–933.

Hashimoto, T., Elder, C.M., Okun, M.S., Patrick, S.K., and Vitek, J.L. (2003). Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J. Neurosci. *23*, 1916–1923.

Heath, R.G. (1963). Electrical self-stimulation of the brain in man. Am. J. Psychiatry *120*, 571–577.

Heath, R.G., Monroe, R.R., and Mickle, W.A. (1955). Stimulation of the amygdaloid nucleus in a schizophrenic patient. Am. J. Psychiatry *111*, 862–863.

Hely, M.A., Morris, J.G., Traficante, R., Reid, W.G., O'Sullivan, D.J., and Williamson, P.M. (1999). The sydney multicentre study of Parkinson's disease: progression and mortality at 10 years. J. Neurol. Neurosurg. Psychiatry *67*, 300–307.

Hely, M.A., Morris, J.G., Reid, W.G., and Trafficante, R. (2005). Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov. Disord. *20*, 190–199.

Henderson, J.M. (2008). Peripheral nerve stimulation for chronic pain. Curr. Pain Headache Rep. *12*, 28–31.

Herholz, K., Carter, S.F., and Jones, M. (2007). Positron emission tomography imaging in dementia. Br. J. Radiol. *80*(Spec No 2), S160–S167.

Hescham, S., Lim, L.W., Jahanshahi, A., Steinbusch, H.W., Prickaerts, J., Blokland, A., and Temel, Y. (2012). Deep brain stimulation of the forniceal area enhances memory functions in experimental dementia: The role of stimulation parameters. Brain Stimulat. Published online February 24, 2012. http://dx.doi.org/10.1016/j.brs.2012.01.008.

Holtzheimer, P.E., and Mayberg, H.S. (2011). Deep brain stimulation for psychiatric disorders. Annu. Rev. Neurosci. *34*, 289–307.

Holtzheimer, P.E., Kelley, M.E., Gross, R.E., Filkowski, M.M., Garlow, S.J., Barrocas, A., Wint, D., Craighead, M.C., Kozarsky, J., Chismar, R., et al. (2012). Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch. Gen. Psychiatry *69*, 150–158.

Horsley, V. (1890). Remarks on the Surgery of the Central Nervous System. BMJ *2*, 1286–1292.

Hoyer, C., Kranaster, L., Sartorius, A., Hellweg, R., and Gass, P. (2012). Long-term course of brain-derived neurotrophic factor serum levels in a patient treated with deep brain stimulation of the lateral habenula. Neuropsychobiology *65*, 147–152.

Hubble, J.P., Busenbark, K.L., Wilkinson, S., Penn, R.D., Lyons, K., and Koller, W.C. (1996). Deep brain stimulation for essential tremor. Neurology *46*, 1150–1153.

Huff, W., Lenartz, D., Schormann, M., Lee, S.H., Kuhn, J., Koulousakis, A., Mai, J., Daumann, J., Maarouf, M., Klosterkötter, J., and Sturm, V. (2010). Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year. Clin. Neurol. Neurosurg. *112*, 137–143.

Hutchison, W.D., Allan, R.J., Opitz, H., Levy, R., Dostrovsky, J.O., Lang, A.E., and Lozano, A.M. (1998). Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann. Neurol. *44*, 622–628.

Hutchison, W.D., Davis, K.D., Lozano, A.M., Tasker, R.R., and Dostrovsky, J.O. (1999). Pain-related neurons in the human cingulate cortex. Nat. Neurosci. *2*, 403–405.

Isaias, I.U., Alterman, R.L., and Tagliati, M. (2009). Deep brain stimulation for primary generalized dystonia: long-term outcomes. Arch. Neurol. *66*, 465–470.

Jiménez, F., Nicolini, H., Lozano, A.M., Piedimonte, F., Salín, R., and Velasco, F. (2012). Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. World Neurosurg. Published online July 23, 2012. http://dx.doi.org/10.1016/j.wneu.2012.07.010.

Jiménez-Ponce, F., Velasco-Campos, F., Castro-Farfán, G., Nicolini, H., Velasco, A.L., Salín-Pascual, R., Trejo, D., and Criales, J.L. (2009). Preliminary study in patients with obsessive-compulsive disorder treated with electrical stimulation in the inferior thalamic peduncle. Neurosurgery *65*(6, Suppl), 203–209, discussion 209.

Johnson, M.D., Miocinovic, S., McIntyre, C.C., and Vitek, J.L. (2008). Mechanisms and targets of deep brain stimulation in movement disorders. Neurotherapeutics *5*, 294–308.

Jones, D.T., Machulda, M.M., Vemuri, P., McDade, E.M., Zeng, G., Senjem, M.L., Gunter, J.L., Przybelski, S.A., Avula, R.T., Knopman, D.S., et al. (2011). Age-related changes in the default mode network are more advanced in Alzheimer disease. Neurology *77*, 1524–1531.

Juckel, G., Uhl, I., Padberg, F., Brüne, M., and Winter, C. (2009). Psychosurgery and deep brain stimulation as ultima ratio treatment for refractory depression. Eur. Arch. Psychiatry Clin. Neurosci. *259*, 1–7.

Kang, G.A., Heath, S., Rothlind, J., and Starr, P.A. (2011). Long-term follow-up of pallidal deep brain stimulation in two cases of Huntington's disease. J. Neurol. Neurosurg. Psychiatry *82*, 272–277.

Keitner, G.I., and Mansfield, A.K. (2012). Management of treatment-resistant depression. Psychiatr. Clin. North Am. *35*, 249–265.

Kennedy, S.H., Lam, R.W., Cohen, N.L., and Ravindran, A.V.; CANMAT Depression Work Group. (2001). Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. Can. J. Psychiatry *46*(*Suppl 1*), 38S–58S.

Kennedy, S.H., Giacobbe, P., Rizvi, S.J., Placenza, F.M., Nishikawa, Y., Mayberg, H.S., and Lozano, A.M. (2011). Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. Am. J. Psychiatry *168*, 502–510.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., and Wang, P.S.; National Comorbidity Survey Replication. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA *289*, 3095–3105.

Koller, W., Pahwa, R., Busenbark, K., Hubble, J., Wilkinson, S., Lang, A., Tuite, P., Sime, E., Lazano, A., Hauser, R., et al. (1997). High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann. Neurol. *42*, 292–299.

Koller, W.C., Lyons, K.E., Wilkinson, S.B., Troster, A.I., and Pahwa, R. (2001). Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov. Disord. *16*, 464–468.

Kringelbach, M.L., Green, A.L., Owen, S.L., Schweder, P.M., and Aziz, T.Z. (2010). Sing the mind electric - principles of deep brain stimulation. Eur. J. Neurosci. *32*, 1070–1079.

Kühn, S., and Gallinat, J. (2011). Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr. Bull. Published online November 10, 2011. http://dx.doi.org/10.1093/schbul/sbr151.

Kühn, A.A., Kempf, F., Brücke, C., Gaynor Doyle, L., Martinez-Torres, I., Pogosyan, A., Trottenberg, T., Kupsch, A., Schneider, G.H., Hariz, M.I., et al. (2008). High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. J. Neurosci. *28*, 6165–6173.

Kuhn, J., Gründler, T.O., Bauer, R., Huff, W., Fischer, A.G., Lenartz, D., Maarouf, M., Bührle, C., Klosterkötter, J., Ullsperger, M., and Sturm, V. (2011). Successful deep brain stimulation of the nucleus accumbens in severe alcohol dependence is associated with changed performance monitoring. Addict. Biol. *16*, 620–623.

Kumar, R., Dagher, A., Hutchison, W.D., Lang, A.E., and Lozano, A.M. (1999). Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. Neurology *53*, 871–874.

Kumar, R., Lozano, A.M., Sime, E., and Lang, A.E. (2003). Long-term follow-up of thalamic deep brain stimulation for essential and parkinsonian tremor. Neurology *61*, 1601–1604.

Kupfer, D.J., Frank, E., and Phillips, M.L. (2012). Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet *379*, 1045–1055.

Lang, A.E., and Lozano, A.M. (1998). Parkinson's disease. First of two parts. N. Engl. J. Med. *339*, 1044–1053.

Laplane, D., Levasseur, M., Pillon, B., Dubois, B., Baulac, M., Mazoyer, B., Tran Dinh, S., Sette, G., Danze, F., and Baron, J.C. (1989). Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. A neuropsychological, magnetic resonance imaging and positron tomography study. Brain *112*, 699–725.

Laxton, A.W., Tang-Wai, D.F., McAndrews, M.P., Zumsteg, D., Wennberg, R., Keren, R., Wherrett, J., Naglie, G., Hamani, C., Smith, G.S., and Lozano, A.M. (2010). A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann. Neurol. *68*, 521–534.

Lee, K.H., Chang, S.Y., Roberts, D.W., and Kim, U. (2004). Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J. Neurosurg. *101*, 511–517.

Leehey, M.A., Munhoz, R.P., Lang, A.E., Brunberg, J.A., Grigsby, J., Greco, C., Jacquemont, S., Tassone, F., Lozano, A.M., Hagerman, P.J., and Hagerman, R.J. (2003). The fragile X premutation presenting as essential tremor. Arch. Neurol. *60*, 117–121.

Lenz, F.A., Jaeger, C.J., Seike, M.S., Lin, Y.C., Reich, S.G., DeLong, M.R., and Vitek, J.L. (1999). Thalamic single neuron activity in patients with dystonia: dystonia-related activity and somatic sensory reorganization. J. Neurophysiol. *82*, 2372–2392.

Limousin, P., Krack, P., Pollak, P., Benazzouz, A., Ardouin, C., Hoffmann, D., and Benabid, A.L. (1998). Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N. Engl. J. Med. *339*, 1105–1111.

Lipsman, N., and Glannon, W. (2012). Brain, mind and machine: What are the implications of deep brain stimulation for perceptions of personal identity, agency and free will? Bioethics. Published online June 10, 2012. http://dx.doi.org/10.1111/j.1467-8519.2012.01978.x.

Lipsman, N., Bernstein, M., and Lozano, A.M. (2010a). Criteria for the ethical conduct of psychiatric neurosurgery clinical trials. Neurosurg. Focus *29*, E9.

Lipsman, N., McIntyre, R.S., Giacobbe, P., Torres, C., Kennedy, S.H., and Lozano, A.M. (2010b). Neurosurgical treatment of bipolar depression: defining treatment resistance and identifying surgical targets. Bipolar Disord. *12*, 691–701.

Lipsman, N., Mendelsohn, D., Taira, T., and Bernstein, M. (2011). The contemporary practice of psychiatric surgery: results from a survey of North American functional neurosurgeons. Stereotact. Funct. Neurosurg. *89*, 103–110.

Lipsman, N., Giacobbe, P., Bernstein, M., and Lozano, A.M. (2012). Informed consent for clinical trials of deep brain stimulation in psychiatric disease: challenges and implications for trial design. J. Med. Ethics *38*, 107–111.

Lipsman, N., Woodside, B.W., Giacobbe, P., Hamani, C., Carter, J., Norwood, S.J., Sutandar, K., Staab, R., Elias, G., Lyman, C.L., et al. (2013). Deep brain stimulation of the subcallosal cingulate area for treatment-refractory anorexia nervosa: A phase I pilot trial. The Lancet, in press.

Lisman, J. (2012). Excitation, inhibition, local oscillations, or large-scale loops: what causes the symptoms of schizophrenia? Curr. Opin. Neurobiol. *22*, 537–544.

Little, S., and Brown, P. (2012). What brain signals are suitable for feedback control of deep brain stimulation in Parkinson's disease? Ann. N Y Acad. Sci. *1265*, 9–24.

Llinás, R.R., Ribary, U., Jeanmonod, D., Kronberg, E., and Mitra, P.P. (1999). Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc. Natl. Acad. Sci. USA *96*, 15222–15227.

Lozano, A.M., Dostrovsky, J., Chen, R., and Ashby, P. (2002). Deep brain stimulation for Parkinson's disease: disrupting the disruption. Lancet Neurol. *1*, 225–231.

Lozano, A.M., Mayberg, H.S., Giacobbe, P., Hamani, C., Craddock, R.C., and Kennedy, S.H. (2008). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol. Psychiatry *64*, 461–467.

Lozano, A.M., Snyder, B.J., Hamani, C., Hutchison, W.D., and Dostrovsky, J.O. (2010). Basal ganglia physiology and deep brain stimulation. Mov. Disord. *25*(*Suppl 1*), S71–S75.

Lozano, A.M., Giacobbe, P., Hamani, C., Rizvi, S.J., Kennedy, S.H., Kolivakis, T.T., Debonnel, G., Sadikot, A.F., Lam, R.W., Howard, A.K., et al. (2012). A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. J. Neurosurg. *116*, 315–322.

Lyons, K.E., and Pahwa, R. (2008). Deep brain stimulation and tremor. Neurotherapeutics *5*, 331–338.

Maia, T.V., Cooney, R.E., and Peterson, B.S. (2008). The neural bases of obsessive-compulsive disorder in children and adults. Dev. Psychopathol. *20*, 1251–1283.

Mallet, L., Polosan, M., Jaafari, N., Baup, N., Welter, M.L., Fontaine, D., du Montcel, S.T., Yelnik, J., Chéreau, I., Arbus, C., et al.; STOC Study Group. (2008). Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N. Engl. J. Med. *359*, 2121–2134.

Manganas, L.N., Zhang, X., Li, Y., Hazel, R.D., Smith, S.D., Wagshul, M.E., Henn, F., Benveniste, H., Djuric, P.M., Enikolopov, G., and Maletic-Savatic, M. (2007). Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. Science *318*, 980–985.

Massoud, F., and Léger, G.C. (2011). Pharmacological treatment of Alzheimer disease. Can. J. Psychiatry *56*, 579–588.

Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M.J., Speckens, A., and Phillips, M.L. (2004). Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch. Gen. Psychiatry *61*, 564–576.

Mayberg, H.S. (1997). Limbic-cortical dysregulation: a proposed model of depression. J. Neuropsychiatry Clin. Neurosci. *9*, 471–481.

Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., and Kennedy, S.H. (2005). Deep brain stimulation for treatment-resistant depression. Neuron *45*, 651–660.

Mazars, G.J. (1975). Intermittent stimulation of nucleus ventralis posterolateralis for intractable pain. Surg. Neurol. *4*, 93–95.

McGuire, J.F., Lewin, A.B., Horng, B., Murphy, T.K., and Storch, E.A. (2012). The nature, assessment, and treatment of obsessive-compulsive disorder. Postgrad. Med. *124*, 152–165.

McIntyre, C.C., and Hahn, P.J. (2010). Network perspectives on the mechanisms of deep brain stimulation. Neurobiol. Dis. *38*, 329–337.

McIntyre, C.C., Savasta, M., Kerkerian-Le Goff, L., and Vitek, J.L. (2004). Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin. Neurophysiol. *115*, 1239–1248.

Mendelsohn, D., Lipsman, N., and Bernstein, M. (2010). Neurosurgeons' perspectives on psychosurgery and neuroenhancement: a qualitative study at one center. J. Neurosurg. *113*, 1212–1218.

Mikati, M.A., Yehya, A., Darwish, H., Karam, P., and Comair, Y. (2009). Deep brain stimulation as a mode of treatment of early onset pantothenate kinase-associated neurodegeneration. Eur. J. Paediatr. Neurol. *13*, 61–64.

Milad, M.R., and Rauch, S.L. (2012). Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn. Sci. *16*, 43–51.

Mink, J.W. (1996). The basal ganglia: focused selection and inhibition of competing motor programs. Prog. Neurobiol. *50*, 381–425.

Mitchell, S.J., Richardson, R.T., Baker, F.H., and DeLong, M.R. (1987). The primate globus pallidus: neuronal activity related to direction of movement. Exp. Brain Res. *68*, 491–505.

Moniz, E. (1936). Tentatives Opératoires dans le Traitement de Certaines Psychoses (Tentative Methods in the Treatment of Certain Psychoses) (Paris: Masson).

Montgomery, E.B., Jr. (2006). Effects of GPi stimulation on human thalamic neuronal activity. Clin. Neurophysiol. *117*, 2691–2702.

Montgomery, E.B., Jr., and Gale, J.T. (2008). Mechanisms of action of deep brain stimulation(DBS). Neurosci. Biobehav. Rev. *32*, 388–407.

Moro, E., Lang, A.E., Strafella, A.P., Poon, Y.Y., Arango, P.M., Dagher, A., Hutchison, W.D., and Lozano, A.M. (2004). Bilateral globus pallidus stimulation for Huntington's disease. Ann. Neurol. *56*, 290–294.

Okun, M.S., Mann, G., Foote, K.D., Shapira, N.A., Bowers, D., Springer, U., Knight, W., Martin, P., and Goodman, W.K. (2007). Deep brain stimulation in the internal capsule and nucleus accumbens region: responses observed during active and sham programming. J. Neurol. Neurosurg. Psychiatry *78*, 310–314.

Olds, J., and Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J. Comp. Physiol. Psychol. *47*, 419–427.

Oyama, G., Foote, K.D., Jacobson, C.E., 4th, Velez-Lago, F., Go, C., Limotai, N., Zeilman, P.R., Romrell, J., Wu, S.S., Neal, D., and Okun, M.S. (2012). GPi and STN deep brain stimulation can suppress dyskinesia in Parkinson's disease. Parkinsonism Relat. Disord. *18*, 814–818.

Pahapill, P.A., and Lozano, A.M. (2000). The pedunculopontine nucleus and Parkinson's disease. Brain *123*, 1767–1783.

Palazidou, E. (2012). The neurobiology of depression. Br. Med. Bull. *101*, 127–145.

Paradiso, G., Cunic, D., Saint-Cyr, J.A., Hoque, T., Lozano, A.M., Lang, A.E., and Chen, R. (2004). Involvement of human thalamus in the preparation of self-paced movement. Brain *127*, 2717–2731.

Perani, D., Colombo, C., Bressi, S., Bonfanti, A., Grassi, F., Scarone, S., Bellodi, L., Smeraldi, E., and Fazio, F. (1995). [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. Br. J. Psychiatry *166*, 244–250.

Pereira, E.A., Muthusamy, K.A., De Pennington, N., Joint, C.A., and Aziz, T.Z. (2008). Deep brain stimulation of the pedunculopontine nucleus in Parkinson's disease. Preliminary experience at Oxford. Br. J. Neurosurg. *22*(*Suppl 1*), S41–S44.

Pereira, E.A., Nandi, D., Jenkinson, N., Stein, J.F., Green, A.L., and Aziz, T.Z. (2011). Pedunculopontine stimulation from primate to patient. J. Neural Transm. *118*, 1453–1460.

Pizzagalli, D.A. (2011). Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology *36*, 183–206.

Porta, M., Servello, D., Zanaboni, C., Anasetti, F., Menghetti, C., Sassi, M., and Robertson, M.M. (2012). Deep brain stimulation for treatment of refractory Tourette syndrome: long-term follow-up. Acta Neurochir. (Wien) *154*, 2029–2041.

Prescott, I.A., Dostrovsky, J.O., Moro, E., Hodaie, M., Lozano, A.M., and Hutchison, W.D. (2009). Levodopa enhances synaptic plasticity in the substantia nigra pars reticulata of Parkinson's disease patients. Brain *132*, 309–318.

Price, J.L., and Drevets, W.C. (2010). Neurocircuitry of mood disorders. Neuropsychopharmacology *35*, 192–216.

Price, J.L., and Drevets, W.C. (2012). Neural circuits underlying the pathophysiology of mood disorders. Trends Cogn. Sci. *16*, 61–71.

Puigdemont, D., Pérez-Egea, R., Portella, M.J., Molet, J., de Diego-Adeliño, J., Gironell, A., Radua, J., Gómez-Anson, B., Rodríguez, R., Serra, M., et al. (2011). Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. Int. J. Neuropsychopharmacol. *22*, 1–13.

Rabins, P., Appleby, B.S., Brandt, J., DeLong, M.R., Dunn, L.B., Gabriëls, L., Greenberg, B.D., Haber, S.N., Holtzheimer, P.E., 3rd, Mari, Z., et al. (2009). Scientific and ethical issues related to deep brain stimulation for disorders of mood, behavior, and thought. Arch. Gen. Psychiatry *66*, 931–937.

Ranck, J.B., Jr. (1975). Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res. *98*, 417–440.

Richardson, D.E., and Akil, H. (1977). Pain reduction by electrical brain stimulation in man. Part 1: Acute administration in periaqueductal and periventricular sites. J. Neurosurg. *47*, 178–183.

Sartorius, A., Kiening, K.L., Kirsch, P., von Gall, C.C., Haberkorn, U., Unterberg, A.W., Henn, F.A., and Meyer-Lindenberg, A. (2010). Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. Biol. Psychiatry *67*, e9–e11.

Savica, R., Matsumoto, J.Y., Josephs, K.A., Ahlskog, J.E., Stead, M., Lee, K.H., and Klassen, B.T. (2011). Deep brain stimulation in benign tremulous parkinsonism. Arch. Neurol. *68*, 1033–1036.

Saxena, S., Brody, A.L., Maidment, K.M., Dunkin, J.J., Colgan, M., Alborzian, S., Phelps, M.E., and Baxter, L.R., Jr. (1999). Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. Neuropsychopharmacology *21*, 683–693.

Saxena, S., Brody, A.L., Maidment, K.M., Smith, E.C., Zohrabi, N., Katz, E., Baker, S.K., and Baxter, L.R., Jr. (2004). Cerebral glucose metabolism in obsessive-compulsive hoarding. Am. J. Psychiatry *161*, 1038–1048.

Schaltenbrand, G. (1965). The effects of stereotactic electrical stimulation in the depth of the brain. Brain *88*, 835–840.

Schermer, M. (2011). Ethical issues in deep brain stimulation. Front Integr. Neurosci. *5*, 17.

Schlaepfer, T.E., and Fins, J.J. (2010). Deep brain stimulation and the neuroethics of responsible publishing: when one is not enough. JAMA *303*, 775–776.

Schlaepfer, T.E., Cohen, M.X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., Joe, A.Y., Kreft, M., Lenartz, D., and Sturm, V. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology *33*, 368–377.

Schwindt, G.C., Chaudhary, S., Crane, D., Ganda, A., Masellis, M., Grady, C.L., Stefanovic, B., and Black, S.E. (2012). Modulation of the default-mode network between rest and task in Alzheimer's disease. Cereb. Cortex. Published online June 12, 2012. http://dx.doi.org/10.1093/cercor/bhs160.

Senova, S., Jarraya, B., Iwamuro, H., Tani, N., Ouerchefani, N., Lepetit, H., Gurruchaga, J.M., Brugières, P., Apartis, E., de Broucker, T., and Palfi, S. (2012). Unilateral thalamic stimulation safely improved fragile X-associated tremor ataxia: a case report. Mov. Disord. *27*, 797–799.

Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., Mintun, M.A., Wang, S., Coalson, R.S., and Raichle, M.E. (2009). The default mode network and self-referential processes in depression. Proc. Natl. Acad. Sci. USA *106*, 1942–1947.

Shen, K.Z., Zhu, Z.T., Munhall, A., and Johnson, S.W. (2003). Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. Synapse *50*, 314–319.

Sheth, S.A., Mian, M.K., Patel, S.R., Asaad, W.F., Williams, Z.M., Dougherty, D.D., Bush, G., and Eskandar, E.N. (2012). Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. Nature *488*, 218–221.

Shin, L.M., and Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology *35*, 169–191.

Shon, Y.M., Lee, K.H., Goerss, S.J., Kim, I.Y., Kimble, C., Van Gompel, J.J., Bennet, K., Blaha, C.D., and Chang, S.Y. (2010). High frequency stimulation of the subthalamic nucleus evokes striatal dopamine release in a large animal model of human DBS neurosurgery. Neurosci. Lett. *475*, 136–140.

Silberstein, P., Kühn, A.A., Kupsch, A., Trottenberg, T., Krauss, J.K., Wöhrle, J.C., Mazzone, P., Insola, A., Di Lazzaro, V., Oliviero, A., et al. (2003). Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. Brain *126*, 2597–2608.

Smith, G.S., Laxton, A.W., Tang-Wai, D.F., McAndrews, M.P., Diaconescu, A.O., Workman, C.I., and Lozano, A.M. (2012). Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. Arch. Neurol. *69*, 1141–1148.

Spiegel, E.A., Wycis, H.T., Marks, M., and Lee, A.J. (1947). Stereotaxic apparatus for operations on the human brain. Science *106*, 349–350.

Sporns, O. (2011). The non-random brain: efficiency, economy, and complex dynamics. Front. Comput. Neurosci. *5*, 5.

Sporns, O., Tononi, G., and Edelman, G.M. (2002). Theoretical neuroanatomy and the connectivity of the cerebral cortex. Behav. Brain Res. *135*, 69–74.

Stavrinou, L.C., Boviatsis, E.J., Stathis, P., Leonardos, A., Panourias, I.G., and Sakas, D.E. (2012). Sustained relief after discontinuation of DBS for dystonia: implications for the possible role of synaptic plasticity and cortical reorganization. J. Neurol. Surg. A Cent. Eur. Neurosurg. *73*, 175–178, discussion 178–179.

Stefani, A., Fedele, E., Galati, S., Pepicelli, O., Frasca, S., Pierantozzi, M., Peppe, A., Brusa, L., Orlacchio, A., Hainsworth, A.H., et al. (2005). Subthalamic

stimulation activates internal pallidus: evidence from cGMP microdialysis in PD patients. Ann. Neurol. *57*, 448–452.

Stefani, A., Lozano, A.M., Peppe, A., Stanzione, P., Galati, S., Tropepi, D., Pierantozzi, M., Brusa, L., Scarnati, E., and Mazzone, P. (2007). Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain *130*, 1596–1607.

Stone, S.S., Teixeira, C.M., Devito, L.M., Zaslavsky, K., Josselyn, S.A., Lozano, A.M., and Frankland, P.W. (2011a). Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. J. Neurosci. *31*, 13469–13484.

Stone, S.S., Teixeira, C.M., Zaslavsky, K., Wheeler, A.L., Martinez-Canabal, A., Wang, A.H., Sakaguchi, M., Lozano, A.M., and Frankland, P.W. (2011b). Functional convergence of developmentally and adult-generated granule cells in dentate gyrus circuits supporting hippocampus-dependent memory. Hippocampus *21*, 1348–1362.

Suthana, N., Haneef, Z., Stern, J., Mukamel, R., Behnke, E., Knowlton, B., and Fried, I. (2012). Memory enhancement and deep-brain stimulation of the entorhinal area. N. Engl. J. Med. *366*, 502–510.

Swedo, S.E., Pietrini, P., Leonard, H.L., Schapiro, M.B., Rettew, D.C., Goldberger, E.L., Rapoport, S.I., Rapoport, J.L., and Grady, C.L. (1992). Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. Arch. Gen. Psychiatry *49*, 690–694.

Thevathasan, W., Pogosyan, A., Hyam, J.A., Jenkinson, N., Foltynie, T., Limousin, P., Bogdanovic, M., Zrinzo, L., Green, A.L., Aziz, T.Z., and Brown, P. (2012). Alpha oscillations in the pedunculopontine nucleus correlate with gait performance in parkinsonism. Brain *135*, 148–160.

Toda, H., Hamani, C., Fawcett, A.P., Hutchison, W.D., and Lozano, A.M. (2008). The regulation of adult rodent hippocampal neurogenesis by deep brain stimulation. J. Neurosurg. *108*, 132–138.

Toleikis, J.R., Metman, L.V., Pilitsis, J.G., Barborica, A., Toleikis, S.C., and Bakay, R.A. (2012). Effect of intraoperative subthalamic nucleus DBS on human single-unit activity in the ipsilateral and contralateral subthalamic nucleus. J. Neurosurg. *116*, 1134–1143.

Turnbull, I.M., McGeer, P.L., Beattie, L., Calne, D., and Pate, B. (1985). Stimulation of the basal nucleus of Meynert in senile dementia of Alzheimer's type. A preliminary report. Appl. Neurophysiol. *48*, 216–221.

Uitti, R.J. (2012). Tandem deep brain stimulation—challenging new structural targets for Parkinson's disease. Parkinsonism Relat. Disord. *18*(*Suppl 1*), S171–S173.

Vandewalle, V., van der Linden, C., Groenewegen, H.J., and Caemaert, J. (1999). Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. Lancet *353*, 724.

Vidailhet, M., Vercueil, L., Houeto, J.L., Krystkowiak, P., Benabid, A.L., Cornu, P., Lagrange, C., Tézenas du Montcel, S., Dormont, D., Grand, S., et al.; French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group. (2005). Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N. Engl. J. Med. *352*, 459–467.

Vitek, J.L., Zhang, J., Hashimoto, T., Russo, G.S., and Baker, K.B. (2012). External pallidal stimulation improves parkinsonian motor signs and modulates neuronal activity throughout the basal ganglia thalamic network. Exp. Neurol. *233*, 581–586.

Wadia, P.M., Lim, S.Y., Lozano, A.M., Adams, J.R., Poon, Y.Y., Torres Diaz, C.V., and Moro, E. (2010). Bilateral pallidal stimulation for x-linked dystonia parkinsonism. Arch. Neurol. *67*, 1012–1015.

Walker, R.H., Koch, R.J., Moore, C., and Meshul, C.K. (2009). Subthalamic nucleus stimulation and lesioning have distinct state-dependent effects upon striatal dopamine metabolism. Synapse *63*, 136–146.

Wichmann, T., and Delong, M.R. (2007). Anatomy and physiology of the basal ganglia: relevance to Parkinson's disease and related disorders. Handb. Clin. Neurol. *83*, 1–18.

Wichmann, T., DeLong, M.R., Guridi, J., and Obeso, J.A. (2011). Milestones in research on the pathophysiology of Parkinson's disease. Mov. Disord. *26*, 1032–1041.

Wilcox, R.A., Cole, M.H., Wong, D., Coyne, T., Silburn, P., and Kerr, G. (2011). Pedunculopontine nucleus deep brain stimulation produces sustained improvement in primary progressive freezing of gait. J. Neurol. Neurosurg. Psychiatry *82*, 1256–1259.

Windels, F., Carcenac, C., Poupard, A., and Savasta, M. (2005). Pallidal origin of GABA release within the substantia nigra pars reticulata during high-frequency stimulation of the subthalamic nucleus. J. Neurosci. *25*, 5079–5086.

World Health Organization (2004). The Global Burden of Disease: 2004 Update. http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf.

Wu, Y.R., Levy, R., Ashby, P., Tasker, R.R., and Dostrovsky, J.O. (2001). Does stimulation of the GPi control dyskinesia by activating inhibitory axons? Mov. Disord. *16*, 208–216.

Zaghloul, K.A., Blanco, J.A., Weidemann, C.T., McGill, K., Jaggi, J.L., Baltuch, G.H., and Kahana, M.J. (2009). Human substantia nigra neurons encode unexpected financial rewards. Science *323*, 1496–1499.

Zhang, K., Bhatia, S., Oh, M.Y., Cohen, D., Angle, C., and Whiting, D. (2010). Long-term results of thalamic deep brain stimulation for essential tremor. J. Neurosurg. *112*, 1271–1276.